Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Anderson EJ, Rouphael NG, Widge AT, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med. DOI: 10.1056/NEJMoa2028436

Table of Contents

mRNA-1273 Study Group
(listed in pubmed, and ordered alphabetically by institutional affiliation)

The following study group members were all closely involved with the design, implementation, and oversight of the mRNA-1273 clinical trial.

Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD. Jae Arega, M.S., John H. Beigel, M.D., Wendy Buchanan, M.S., B.S.N., Mohammed Elsafy, M.D., Binh Hoang, Pharm.D., Sonnie Kim, M.Sc., Aparna Kolhekar, Ph.D., Hyung Koo, B.S.N., Catherine Luke, Ph.D., Mamodikoe Makhene, M.D., M.P.H., Seema Nayak, M.D., Rhonda Pikaart-Tautges, B.S., Paul C. Roberts, Ph.D., Janie Russell, B.S., Elisa Sindall, B.S.N.

The Emmes Company, LLC, Rockville, MD. Jim Albert, M.S., Kaitlyn Cross, M.S., Mat Makowski, Ph.D.

Emory University School of Medicine, Atlanta, GA. Evan J. Anderson, M.D., Amer Bechnak, M.D., Mary Bower, R.N., Andres F. Camacho-Gonzalez, M.D., M.Sc., Matthew Collins, M.D., Ph.D., Ana Drobeniuc, M.P.H., Venkata Viswanadh Edara, Ph.D., Srilatha Edupuganti, M.D., M.P.H, Katharine Floyd, Theda Gibson, M.S., Cassie M. Grimsley Ackerley, M.D., Brandi Johnson, Satoshi Kamidani, M.D., Carol Kao, M.D.; Colleen Kelley, M.D., M.P.H., Hollie Macenczak, R.N., Michele Paine McCullough, M.P.H., , Etza Peters, R.N., Varun K. Phadke, M.D., Christina A. Rostad, M.D., Nadine Rouphael, M.D., Erin Scherer Ph.D., D.Phil., Amy Sherman, M.D., Kathy Stephens, R.N., Mehul S. Suthar, Ph.D., Mehgan Teherani, M.D., M.S., Jessica Traenkner, P.A., Cynthia Whitney, M.D., Juton Winston, Inci Yildirim, M.D., Ph.D.

Kaiser Permanente Washington Health Research Institute, Seattle, WA. Barbara A. Carste, M.P.H, Maya B. Dunstan, M.S., R.N., Lisa A. Jackson, M.D., M.P.H.

Moderna, Inc., Cambridge, MA. Hamilton Bennett, M.Sc., Nedim Emil Altaras, Ph.D., Andrea Carfi, Ph.D., Marjorie Hurley, Pharm.D., Brett Leav, M.D., Rolando Pajon, Ph.D., Wellington Sun, M.D., Tal Zaks, M.D., Ph.D.

Seattle Children's Research Institute, Seattle, WA. Rhea N. Coler, M.Sc., Ph.D., Sasha E. Larsen, Ph.D.

University of Maryland School of Medicine, Baltimore, MD. Kathleen M. Neuzil, M.D.

University of North Carolina, Durham, NC. Lisa C. Lindesmith, M.S., David R. Martinez, Ph.D., Jennifer Munt, B.S., Michael Mallory, M.P.H., Caitlin Edwards, B.S., Ralph S. Baric, Ph.D.

Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, M.D. Nina M. Berkowitz, M.P.H., Kevin Carlton, M.S., Kizzmekia S. Corbett, Ph.D., Pamela Costner, R.N., B.S.N., Nicole A. Doria-Rose, Ph.D., Britta Flach, Ph.D., Martin Gaudinski, M.D., Ingelise Gordon, R.N., Barney S. Graham, M.D., LaSonji Holman, F.N.P., Julie E. Ledgerwood, D.O., Bob C. Lin, B.S., Mark K. Louder**,** John R. Mascola, M.D., Adrian B. McDermott, Ph.D., Kaitlyn M. Morabito, Ph.D., Laura Novik, R.N., M.A., Sijy O'Dell, M.S., Marcelino Padilla, B.S., Amarendra Pegu, Ph.D, Stephen D. Schmidt, B.S., Phillip A. Swanson II, Ph.D., Lingshu Wang, Ph.D., Alicia T. Widge, M.D., M.S., Eun Sung Yang M.S., Yi Zhang B.S.

Vanderbilt University Medical Center, Nashville, TN. James D. Chappell, M.D., Ph.D., Mark R.

Denison, M.D., Tia Hughes, M.S., Xiaotao Lu, M.S., Andrea J. Pruijssers, Ph.D., Laura J. Stevens, M.S.

Fred Hutchinson Cancer Research Center, Seattle WA. Christine M. Posavad, Ph.D

University of Washington, Seattle, WA. Michael Gale, Jr., Ph.D.

mRNA-1273 Study Team Members

The mRNA-1273 trial was a collective group effort across multiple institutions and locations. Below is a list of sites and staff that significantly contributed to the implementation and conduct of the mRNA-1273 trial (alphabetically by institution).

Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD. Jae Arega, M.S., John H. Beigel, M.D., Wendy Buchanan, M.S., B.S.N., Mohammed Elsafy, M.D., Ranjodh Gill M.P.H, Binh Hoang, Pharm.D., Sonnie Kim, M.Sc., Aparna Kolhekar, Ph.D., Hyung Koo, B.S.N., Marina Lee, Ph.D., Catherine Luke, Ph.D., Mamodikoe Makhene, M.D., M.P.H., Jorge Mejia-Galvis, M.D., Seema Nayak, M.D., Rhonda Pikaart-Tautges, B.S., Paul C. Roberts, Ph.D., Janie Russell, B.S., Elisa Sindall, B.S.N.

The Emmes Company, LLC, Rockville, MD. Jim Albert, M.S., Kaitlyn Cross, M.S., Cassandra Karcs, M.P.H., Pratap Kunwar, M.S., Mat Makowski, Ph.D., Ava Manokian, B.A., Eli Sendra, M.S., Semhal Selamawi, B.A.

Emory University School of Medicine, Atlanta, GA. Alexis Ahonen, N.P., Ghina Alaaeddine, M.D., LaCarles Allen, Evan J. Anderson, M.D., Larry Anderson, M.D., Teresa Ball, R.N., Richard L. Bearden II, Amer Bechnak, M.D., Mary Bower, R.N., Sydney Biccum, Laurel Bristow, M.P.H, Andres F. Camacho-Gonzalez, M.D., M.Sc., Xuemin Chen, M.D., M.S., Laura Clegg, R.N., Matthew Collins, M.D., Ph.D., Ana Drobeniuc, M.P.H., Francine Dyer, R.N., Venkata Viswanadh Edara, Ph.D., Srilatha Edupuganti, M.D., M.P.H., Katharine Floyd, Theda Gibson, M.S., Felicia Glover, Cassie M. Grimsley Ackerley, M.D., Lisa Harewood, Laila Hussaini, M.P.H., Hui-Mien Hsiao, M.S., Brandi Johnson, Satoshi Kamidani, M.D., Carol Kao, M.D., Colleen Kelley, M.D., M.P.H., Peggy Kettle, R.N., Wensheng Li, M.S., Cindy Lubbers, R.N., Hollie Macenczak, R.N., Lisa Macoy, M.S.N., R.N., Michele Paine McCullough, M.P.H., Amy Muchinsky, G. Osinski, Amanda Panepento, Etza Peters, R.N., Varun K. Phadke, M.D., Brittany Robinson, Susan Rogers, R.Ph., Christina Rostad, M.D., Nadine Rouphael, M.D., Youssef Saklawi, M.D., Amber Samuel, Erin Scherer, Ph.D., D.Phil., Amy Sherman, M.D., Oliver Smith, M.S., Kathleen Stephens, R.N., Mehgan Teherani, M.D., M.S., Ashley Tippett,, M.P.H., Sean Todd, Jessica Traenkner, P.A., Dongli Wang, Cynthia Whitney, M.D., Juton Winston, Terra Jean Winter, Jianguo Xu, Ph.D., RPh, Yongxian Xu, M.D., Inci Yildirim, M.D., Ph.D., and Kathryn Zaks, M.S.

Kaiser Permanente Washington Health Research Institute, Seattle, WA. Lee Barr, R.N., Joyce Benoit, R.N., Heather Beseler, M.B.A., Rachael Burganowski, M.S., Barbara Carste, M.P.H., Joe Choe, B.S., John Dunn, M.D., M.P.H., Maya Dunstan, M.S., R.N., Roxanne Erolin, M.P.H., Jana ffitch, L.P.N., Colin Fields, M.D., Lisa A. Jackson, M.D., Erika Kiniry, M.P.H., De Vona Lang, L.M.P., Susan Lasicka, R.Ph., Stella Lee, B.A., Matthew Nguyen, M.P.H., Jennifer Nielsen, M.N., A.R.N.P., Hallie Phillips, M.ed., Stephanie Pimienta, B.S., David Skatula, R.Ph., Janice Suyehira, M.D., Karen Wilkinson, M.N., A.R.N.P., Michael Witte, Pharm.D.

Moderna, Inc., Cambridge, MA. Nedim Emil Altaras, Ph.D., Hamilton Bennett, M.Sc., Andrea Carfi, Ph.D., Marjorie Hurley, Pharm.D., Brett Leav, M.D., Rodrigo Laureano, M.S., Rolando Pajon, Ph.D., Wellington Sun, M.D., Tal Zaks, M.D., Ph.D. The Moderna Technical Development and Manufacturing Technical Operations Team.

Seattle Children's Research Institute, Seattle, WA. Rhea N. Coler, M.Sc., Ph.D., Sasha E. Larsen, Ph.D., Tiffany Pecor, B.S., Brian Granger, B.S., L.A.T., Valerie A. Reese, M.S., Evan Cross, B.Sc., Susan L. Baldwin, Ph.D., James M. Ferrenberg M.B., (ASCP) CM, Bryan Berube, Ph.D.

University of Maryland School of Medicine, Baltimore, MD. Kathleen M. Neuzil, M.D.

University of North Carolina, Durham, NC. Lisa C. Lindesmith, M.S., David R. Martinez, Ph.D., Jennifer Munt, B.S., Michael Mallory, M.P.H., Caitlin Edwards, B.S., Ralph S. Baric, Ph.D.

Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD. Charla Andrews, M.S., Sc.M., Preeti Apte, B.A., Anita Arthur, R.N., B.S.N., Allison Beck, M.P.A.S., P.A.C., Nina M. Berkowitz, M.P.H., Seyhan Boyoglu-Barnum, Ph.D., Eugeania Burch, M.P.H., Kevin Carlton, M.S., Cora Trelles Cartagena, M.P.H., Joe Casazza, M.D., Ph.D., Emily Coates, Ph.D., Kizzmekia S. Corbett, Ph.D., Pamela Costner, R.N., B.S.N., Jennifer Cunningham, R.N., B.S.N., Nicole A. Doria-Rose, Ph.D., Aba Eshun, R.N., B.S.N., Catina Evans, Britta Flach, Ph.D., Martin Gaudinski, M.D., Rebecca A. Gillespie, B.S., Ingelise Gordon, R.N., Barney S. Graham, M.D., Carmencita S Graves M.S., M.B.A., Mercy Guech, Ph.D., Cynthia Starr Hendel, C.R.N.P., Renunda Hicks, LaSonji Holman, F.N.P., Kate Houser, Ph.D., Justine Jones, B.S., Brenda Larkin, R.N., B.S.N., Lam Le, M.B.A., Julie E. Ledgerwood, D.O., Bob C. Lin, B.S., Lauren Lizewski, M.P.H., Mark K. Louder, John R. Mascola, M.D., Adrian B. McDermott, Ph.D., Floreliz Mendoza, R.N., John Misasi, M.D., Kaitlyn M. Morabito, Ph.D., Patricia Morgan, P.A., M.Sc., Thuy Nguyen, B.A., Laura Novik, R.N., M.A., Mark O'Callahan, B.S., Sijy O'Dell, M.S., Abidemi Ola, M.S.N., F.N.P.-C., Marcelino Padilla, B.S., Karen Parker, D.N.P., C.R.N.P., F.N.P.-B.C., Amarendra Pegu, Ph.D, Iris Pittman, B.A., Sarah Plummer, C.R.N.P., La'Shawn Requilman, Ro Rothwell, Ph.D., Jamie Saunders, R.N., B.S.N., Stephen D. Schmidt, B.S., Ellie Seo, R.Ph., Ph.D., Sandra Sitar, M.S., Phillip A. Swanson II, Ph.D., Stephanie Taylor, B.A., Shinyi Telscher, Pharm.D., Colin Tran, B.S., Olga Trofymenko, M.D., Olga Vasilenko, M.S., Xiaolin Wang, R.N., William Whalen, R.N., B.S.N., Pernell Williams, B.A., Eun Sung Yang, M.S., Phillip A. Swanson II, Ph.D., Lingshu Wang, Ph.D., Alicia T. Widge, M.D., M.S., Galina Yamshchikov, M.S., Eun Sung Yang M.S., Kathy Zephir, R.N., B.S.N., M.S., Yi Zhang, B.S.

Vanderbilt University Medical Center, Nashville, TN. James D. Chappell, M.D., Ph.D., Mark R. Denison, M.D., Tia Hughes, M.S., Xiaotao Lu, M.S., Andrea J. Pruijssers, Ph.D., Laura J. Stevens, M.S.

Fred Hutchinson Cancer Research Center, Seattle, WA. Christine M. Posavad, Ph.D.

University of Washington, Seattle WA. Michael Gale, Jr., Ph.D.,

Additional Contributors

Below is a list of sites and staff that contributed serum samples from, and information on, Covid-19 convalescent patients:

University of Washington Department of Medicine, Seattle WA. Helen Chu, M.D, M.P.H.

Aaron Diamond AIDS Research Center and Columbia University, New York NY. David Ho, M.D.

Vanderbilt Institute for Clinical and Translational Research, Nashville TN. Gordon Bernard, M.D.

Supplemental Methods:

Additional Study Procedure Details

Safety laboratory evaluations including white blood cell and platelet counts and levels of hemoglobin, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, and lipase were assessed on the day of and 7 days after each vaccination.

Additional Immunologic Assay Method Details

The NIAID VRC performed the ELISA and PsVNA assays, the University of North Carolina-Chapel Hill (UNC) performed the nLuc HTNA, Emory University performed the FRNT-mNG assay, and Vanderbilt University Medical Center performed PRNT.

SARS-CoV-2 S-2P and RBD ELISA. Briefly, SARS-CoV-2 Spike S-2P antigen [VRC SARS-CoV-2 S-2P (15-1208)-3C-His8-Strep2x2] was coated onto flat bottom 96-well plates overnight at 4°C at a concentration of 2 µg/mL in DPBS. For SARS-CoV-2 RBD (Ragon-SARSCoV-2 S-RBD (319-529)-His8-SBP), 4 µg/mL were used. Proteins were generously produced, purified and provided by Dr. Dominic Esposito (Frederick National Laboratory for Cancer Research, NCI). After incubation, plates were moved to an integrated Beckman Biomek (Indianapolis, IN, USA) automated system.

Plates were washed and blocked (3% milk in PBS with 0.1% Tween 20 (TPBS)) for 1 hour at room temperature. Duplicate 4-fold 8-point serial dilutions (starting at 1:100) of heat-inactivated serum samples diluted in 1% milk in TPBS were added to the wells and incubated at room temperature for 2 hours. Incubation was followed by HRP-labeled goat anti-human IgG (H+L) cross absorbed secondary antibody detection for 1 hour at room temperature. Detection (Thermo Fisher Catalogue # A18811) was used at a 1:32,000 dilution in TPBS. Plates were washed and

100 µL of TMB (DAKO Catalogue # S1599) substrate was added for 15 minutes at room temperature. Color development was stopped by addition of sulfuric acid and plate absorbance was read within 30 minutes at 450 nm and 650 nm via the Molecular Devices Paradigm (San Jose, CA, USA) plate reader.

Endpoint Titer dilution from raw OD data was interpolated using the plate background OD + 10 STDEV by asymmetric sigmoidal 5-pl curve fit of the test sample. In the rare event the asymmetric sigmoidal 5-pl curve failed to interpolate the endpoint titer, a sigmoidal 4-pl curve was used for the analysis. Where the binding responses reached the upper limit of quantitation, the test samples were repeated in an 8-point, 4-fold dilution series starting at 1:5000 and the final reciprocal endpoint titer were reported. Area under the curve (AUC) was calculated with baseline anchored by the plate background OD + 10 STDEV. All statistical analyses were performed using GraphPad Prism, version 8.3.0.

Pseudovirus neutralization assay (PsVNA). Neutralization activity against SARS-2-CoV was measured in a single-round-of-infection assay with pseudotyped virus particles (pseudoviruses). To produce SARS-CoV-2 pseudoviruses, an expression plasmid bearing codon-optimized SARS-CoV-2 full-length S plasmid (parental sequence Wuhan-1, Genbank #: MN908947.3) was co-transfected into HEK293T/17 cells (ATCC#CRL-11268) cells with packaging plasmid pCMVDR8.2, luciferase reporter plasmid pHR′CMV-Luc,[1] and a TMPRSS2 plasmid.[2] To make the pseudoviruses with D614G spike, we used a modified plasmid (gift of David Montefiori): our plasmid bearing codon-optimized CMV/R-SARS-CoV-2 full-length S (parental sequence Wuhan-1, Genbank #MN908947.3) was subjected to site-directed mutagenesis to provide the D614G amino acid change. The plasmid was sequenced to ensure that only this mutation was present. Pseudoviruses were mixed with serial dilutions of sera or antibodies and then added to monolayers of ACE-2-overexpressing 293T cells (gift of Michael Farzan and Huihui Mu), in

triplicate. Three days post infection, cells were lysed, luciferase was activated with the Luciferase Assay System (Promega), and relative light units (RLU) were measured at 570 nm on a Spectramax L luminometer (Molecular Devices). After subtraction of background RLU (uninfected cells), % neutralization was calculated as 100x((virus only control)-(virus plus antibody))/(virus only control). Dose-response curves were generated with a 5-parameter nonlinear function, and titers reported as the serum dilution or antibody concentration required to achieve 50% (50% inhibitory dilution [ID50]) or 80% (80% inhibitory dilution [ID80]) neutralization. The input dilution of serum is 1:20, thus, 20 is the lower limit of quantification. Samples that do not neutralize at the 50% level are expressed as <20 and plotted at half that dilution, *i.e.* 10. If duplicate assays return one value above 20 and <20, the result is reported as the geometric mean of 10 and the positive assay; therefore, some values between 10 and 20 are reported. To monitor for assay quality, the same 6 control samples were included in each assay work session: three negative controls (pre-pandemic human sera collected prior to May 2019) and three sera from SARS-CoV-2 convalescent individuals. Of note, some values reported here for subjects aged 18-55 are different from those reported in Jackson et al.[3] the new values are the geometric mean of routine repeats.

SARS-CoV-2 nanoluciferase high throughput neutralization assay (nLuc HTNA). Vaccinee sera was incubated at 56ºC for 30 min. A full-length SARS-CoV-2 virus based on the Seattle Washington isolate was designed to express nanoluciferase (nLuc) and was recovered via reverse genetics as described previously.[4] The SARS-CoV-2 nLuc virus titer was measured in Vero E6 USAMRIID cells, as defined by plaque forming units (PFU) per mL in a 6-well plate format. For the 96-well neutralization assay, Vero E6 USAMRIID cells were plated at 20,000 cells per well the day prior in clear bottom, black walled plates. Cells were inspected to ensure confluency on the day of the assay. In separate 96-well dilution plates, serum samples were diluted to a starting dilution of 1:20 and were serially diluted 2-fold up to nine dilution spots. Serially

diluted serum samples were mixed in equal volume with live virus for a final starting serum sample dilution of 1:40. Cell and virus only control wells were also included in each 96-well dilution plate. The serum-virus mixture and controls were then incubated at 37ºC with 5% CO_2 for 1 hour. Following incubation, growth media was removed from the clear bottom, black walled 96-well cell plates and the serum-virus mixture was added to the Vero E6 USAMRIID cell plates for a final concentration of 75 plaque forming units (PFU) per well. Following infection, plates were incubated at 37ºC with 5% CO_2 for ~48 hours. After the ~48-hour incubation, cells were lysed, and luciferase activity was measured via Nano-Glo Luciferase Assay System (Promega) according to the manufacturer specifications. Luminescence was measured by a Spectramax M3 plate reader (Molecular Devices, San Jose, CA). SARS-CoV-2 neutralization titers were defined as the sample dilution at which a 50% reduction in RLU was observed relative to the average of the virus control wells (ID50). Both ID50 and ID80 values were reported with the upper limit of quantitation titer at 10,240 and the lower limit of quantitation at a titer of 40. Samples that do not neutralize at the level of detection at 50% were plotted at 20 and was used for geometric mean calculations.

Focus Reduction Neutralization Titer assay (FRNT-mNG). Vaccinee or COVID-19 patient convalescent sera were incubated at 56°C for 30 min and manually diluted in duplicate in serum-free Dulbecco's modified and incubated with 750-1000 focus-forming units of infectious clone derived SARS-CoV-2-mNG virus[5] at 37º C for 1 hour. The virus/serum mixture was added to VeroE6 cell (C1008, ATCC, #CRL-1586) monolayers seeded in 96-well blackout plates and incubated at 37º C for 1 hour. Post incubation, the inoculum was removed and replaced with pre-warmed complete DMEM containing 0.85% methylcellulose. Plates were incubated at 37º C for 24 hours. After 24 hours, the methylcellulose overlay was removed, cells were washed three times with phosphate-buffered saline (PBS), and fixed with 2% paraformaldehyde (PFA) in PBS for 30

minutes at room temperature. The 2% PFA is removed and washed twice with PBS. The foci were visualized using an ELISPOT reader (CTL ImmunoSpot S6 Universal Analyzer) under a FITC channel and enumerated using Viridot[6]. The neutralization titers were calculated as follows: 1 - (ratio of the mean number of foci in the presence of sera and foci at the highest dilution of respective sera sample). Each specimen is tested in two independent assays performed at different times. The FRNT-mNG$_{50}$ and FRNT-mNG$_{80}$ titers were interpolated using a 4-parameter nonlinear regression in GraphPad Prism 8.4.3. Samples that do not neutralize at the limit of detection at 50% are plotted at 10 and was used for geometric mean calculations.

SARS-CoV-2 Plaque-Reduction Neutralization Testing (PRNT). Vaccinee sera were incubated at 56^{o}C for 45 min and manually diluted in gelatin saline (0.3% [wt/vol] gelatin in phosphate-buffered saline supplemented with $CaCl_2$ and $MgCl_2$) to generate a 1:4 dilution of the original specimen, which served as a starting concentration for further serial log_2 dilutions in gelatin saline using an automated liquid handling system. The terminal serum concentration corresponded to 1/131,072 of the original. Antisera were combined with an equal volume of SARS-CoV-2 clinical isolate, SARS-CoV-2/human/USA/USA-WA1/2020 (GenBank: MN985325.1), in gelatin saline, producing an average final virus concentration of 580 plaque-forming units (PFU) per ml in each serum dilution ranging from final concentrations of 1/8 to 1/262,144 of the original. Virus/serum mixtures were incubated for 20 min at 37^{o}C, followed by adsorption of 0.1 ml aliquots to each of two confluent Vero E6 cell monolayers in 10-cm^2 wells for 30 min at 37^{o}C. Four aliquots of untreated (i.e., no serum) control virus were subjected to identical conditions. Cell monolayers were overlaid with Dulbecco's modified Eagle's medium containing 1% agar and incubated for 3 days at 37^{o}C in humidified 5% CO_2. Plaques were enumerated by direct visualization, and the average number of plaques in virus/serum (duplicate) and virus-only (quadruplicate) wells was used to calculate percent neutralization at each serum dilution according to the following formula: 1 - (ratio of mean

number of plaques in the presence and absence of serum). Each specimen was tested in two independent assays performed at different times. Fractional neutralization from duplicate specimens was plotted as a function of $\log_2$ serum dilution, and the dose-response relationship was fit to a five-parameter logistic regression model using the supplementary package nplr[7] in R.[8] $PRNT_{80}$ titers, expressed as the reciprocal of the highest serum dilution reducing virus infectivity by 80%, were calculated from resulting curves. Specimens exhibiting less than 80% inhibitory activity at the lowest dilution tested, 1:8, were assigned a titer of 4.

Four dilutions of a COVID-19 convalescent serum control, spanning a 256-fold concentration range, were included with each performance of PRNT for longitudinal monitoring of assay stability. In addition, duplicate neutralization curves were inspected for agreement relative to expected deviations naturally arising from numerous interacting biological as well as technical variables inherent to PRNT. Unusually large disagreement between duplicate curves was resolved by additional testing.

Antibody Assay Correlation Methods. Spearman correlations were calculated for all post vaccination time points available. Confidence intervals were calculated using the z-transformation.

Intracellular cytokine stimulation (ICS) assay. An ICS assay was used to evaluate T cell responses elicited by the mRNA-1273 vaccine in clinical samples collected on day 1, day 29, and day 43 post-vaccination. Briefly, frozen peripheral blood mononuclear cells were thawed, counted and rested in R10 culture media (90% RPMI 1640 with 10% Fetal Bovine Serum (FBS) and 1% Penicillin Streptomycin and L-Glutamine) overnight at 37°C with 5% CO2. Following the rest period, cells were counted on day 2 and resuspended in R10 cell culture media. 0.5-1.5 x 10^6

cells were transferred to individual wells of a 96-well V-bottom plate(s) and incubated with pools of 15-mer peptides overlapping by 10 amino acids covering the N-terminus of SARS-CoV-2 Spike protein up to the furin cleavage site (S1 pool), the C-terminus of the SARS-CoV-2 Spike protein up to the furin cleavage site (S2 pool) for 6 hours at 37°C with 5% CO2. Peptides pools were custom ordered from JPT (Peptide Technologies GmbH, Berlin, Germany) and were >85% pure. Following stimulation, cells were washed and stained with viability dye for 20 minutes at room temperature, followed by surface stain for 20 minutes at room temperature, cell fixation and permeabilization with BD cytofix/cytoperm kit (catalog # 554714) for 20 minutes at room temperature, and then intracellular stain for 20 minutes at room temperature. Upon completion of staining, cells were collected on a BD FACSymphony Flow Cytometer. Samples were analyzed using FlowJo 10.6.2. Anomalous “bad” events were separated from “good” events using FlowAI.6 “Good events” were used to determine cytokine responses.

Cytokine positive cells were determined by gating on singlets, lymphocytes, viability dye-CD3+, followed by CD4+ or CD8+. Individual cytokines were plotted on the Y-axis vs CD69 on the X-axis and only the CD69+cytokine+ events were used to determine positive responses. Positive cytokine gates were determined using unstimulated samples during qualification testing. A template of gating was created during assay qualification and was applied to all vaccine samples without manipulation. “Any responses” are any combination of the indicated individual cytokines by a population of CD4 or CD8 T cells and were calculated using Boolean combination gates. All antigen-specific cytokine frequencies are reported after background subtraction of identical gates from the same sample incubated with the negative control stimulation (DMSO).

Additional Statistical Methods

The Williams mean was used for AUC data due to presence of points between zero and one. This mean follows the same procedure as above except that one is added to all data points prior to

log-transformation and subtracted after back-transformation. Calculations of quartiles for T-cell boxplots use definition 7 as described by Hyndman and Fan (1996).[9] All other boxplots use definition 2.

Additional Convalescent Sera Description

Convalescent sera were collected from a total of 41 individuals with confirmed Covid-19 diagnosis. These samples were included in convalescent sera panels and tested along with the vaccine trial participant samples as comparators for the ELISA and PsVNA vaccine-induced responses and to establish correlations across the ELISA (S-2P and RBD) and the PsVNA. Binding and PsVNA data are shown for one serum sample from each of the 41 individuals and were previously published in the 18-55 year-old Phase I study of mRNA-1273.[3] The samples were collected under IRB approved protocols at the National Institutes of Health, Bethesda MD (NCT00067054); Aaron Diamond AIDS Research Center, Columbia University, New York NY (NCT04342195); the University of Washington, Seattle WA (HAARVI study and STUDY00000959); and Vanderbilt University Medical Center, Nashville, TN (NCT04362176 and IRB VUMC protocol # 070258). Time since diagnosis (onset of symptoms or positive PCR test) ranged from 23-54 days (median 34 days). Ages ranged from 20-77 years (median 49); 19 were female, 22 were male. Race and ethnicity were reported as follows: 4 were Asian, 2 were Black, 4 were White/Hispanic or Latino, 5 were White/ethnicity unreported, and 26 were White/Not Hispanic or Latino. The Covid-19 illness severity was known for 38 of these individuals and was classified as mild in 63%, moderate in 22%, and severe (hospitalization requiring intensive care and/or ventilation) in 15%.[3]

Supplemental Study Results:

Safety laboratory grade 2 or higher adverse events

Safety laboratory adverse events were graded according to a standard toxicity grading scale. A total of five grade ≥2 safety laboratory adverse events were noted. All were due to abnormalities in the complete blood count (CBC), most commonly a decrease in hemoglobin in 4 subjects in the group 56-70 years of age. The decreases in hemoglobin did not lead to discontinuation of vaccination and were judged to be not clinically significant. Two events were considered related to vaccine, and 2 events were considered unrelated, with an alternative etiology of phlebotomy. One of these decreases in hemoglobin met criteria for a Grade 3 laboratory event upon repeat due to the degree of decrease from baseline and was attributed to vaccine, but was not felt to be clinically significant (Hemoglobin 14.1 grams/dL, in the laboratory normal range). Grade 2 thrombocytopenia was noted in one subject ≥71 years of age.

Unsolicited adverse events

There were 71 unsolicited adverse events reported, none met the definition of a serious adverse event (Table S3). Of those, 61 were mild in severity, of which 16 (26%) were judged related to vaccination, 9 were moderate in severity, of which 1 (11%) was judged related to vaccination (lack of appetite in a subject in the 25 µg dose 56-70 year old cohort), and 1 was a severe event judged unrelated to vaccination (hypoglycemia in a subject in the 100 µg dose 56-70 year cohort that occurred after fasting and vigorous exercise). There was no obvious clustering of events by MedDRA® System Organ Class.

Supplemental Figure 1. CONSORT Flow Diagram

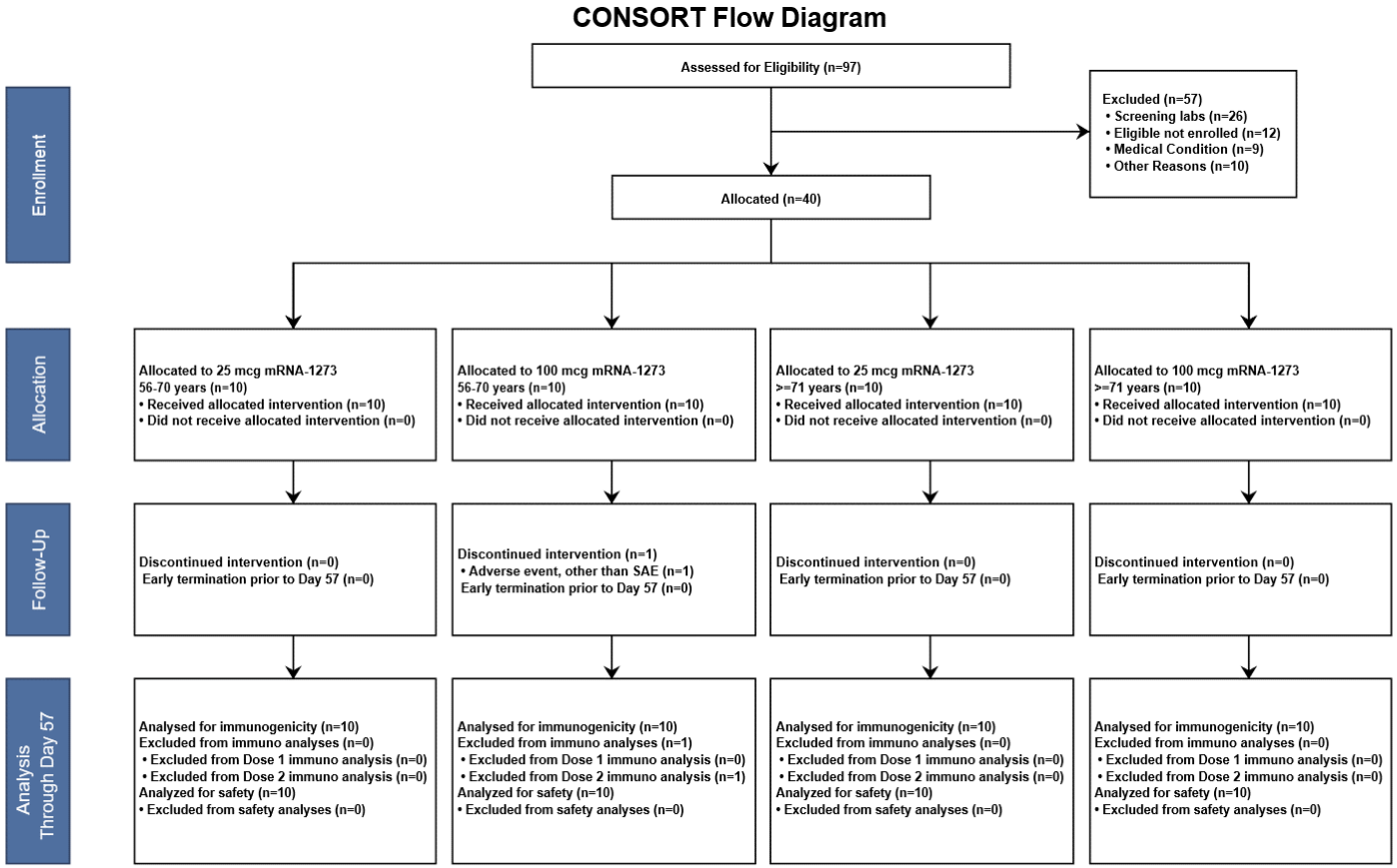
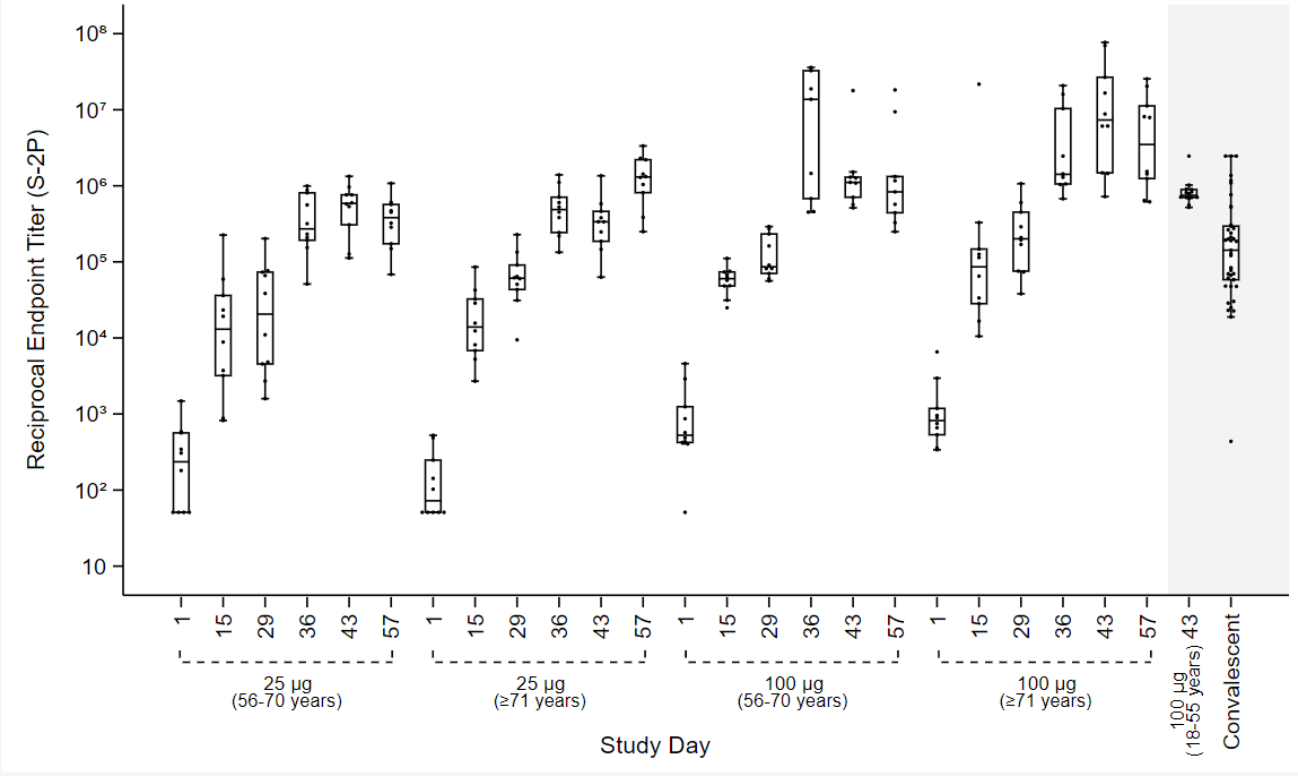


Figure S2. Binding to SARS-CoV-2 spike proteins in ELISA by time point and vaccination group.

Boxes and horizontal bars denote interquartile range (IQR) and median respectively. Whisker endpoints are equal to the maximum and minimum values below or above the median +/- 1.5 x IQR. Data from 18-55 year-old subjects that received a 100 µg dose of mRNA-1273, and convalescent sera from 41 individuals are included for comparison (gray background).[3] Panel **A** represents the Serum S-2P IgG ELISA Endpoint Titers by Time Point and Treatment Group. Panel **B** represents the IgG ELISA binding to S-2P as Area Under the Curve. Ten participants were tested at each time point in these older adults except for 9 participants in the 25 µg 56-70 year-old group beginning at Day 36.

A.



B.

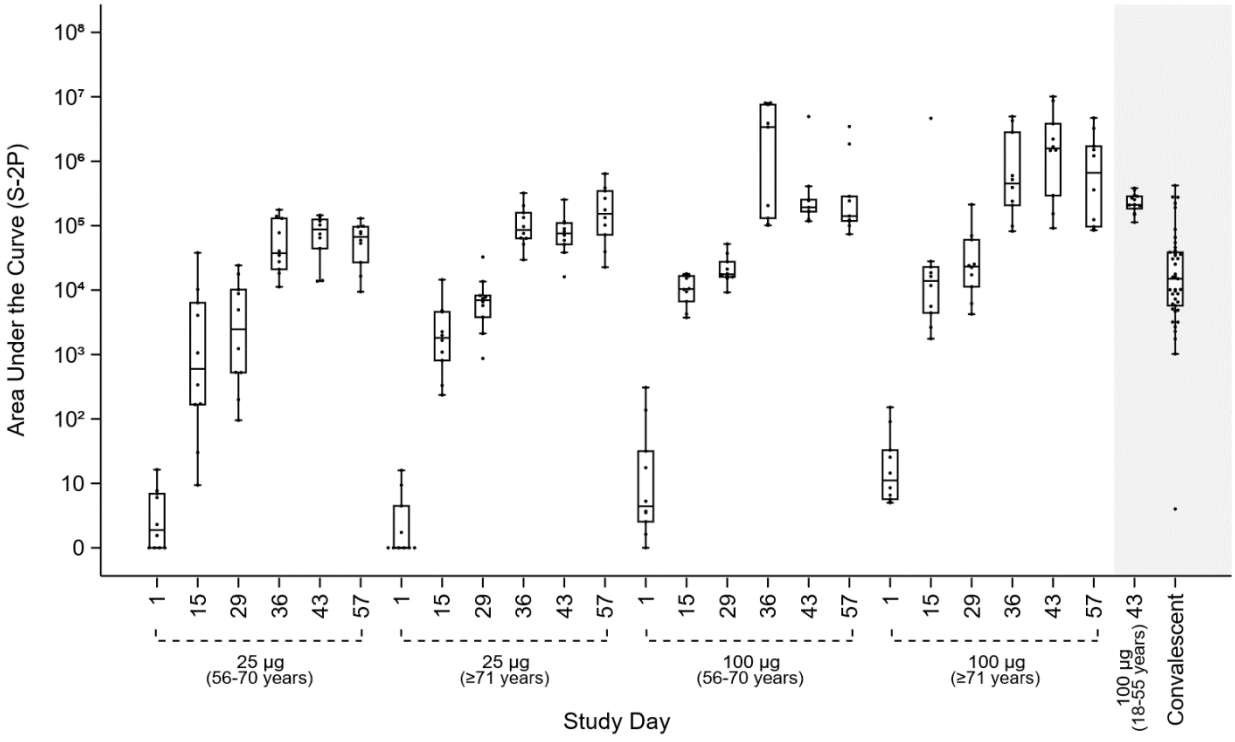

Area Under the Curve (S-2P)
10^8
10^7
10^6
10^5
10^4
10^3
10^2
10
0
1
15
29
36
43
57
25 µg (56-70 years)
25 µg (≥71 years)
100 µg (56-70 years)
100 µg (≥71 years)
100 µg (18-55 years)
Convalescent
Study Day

Figure S3. Binding to RBD in ELISA Area Under the Curve by time point and vaccination group.

Boxes and horizontal bars denote interquartile range (IQR) and median respectively. Whisker endpoints are equal to the maximum and minimum values below or above the median +/- 1.5 x IQR. Data from 18-55 year-old subjects that received a 100 µg dose of mRNA-1273, and convalescent sera from 41 individuals are included for comparison (gray background).[3] Ten participants were tested at each time point in these older adults except for 9 participants in the 25 µg 56-70 year-old group beginning at Day 36.

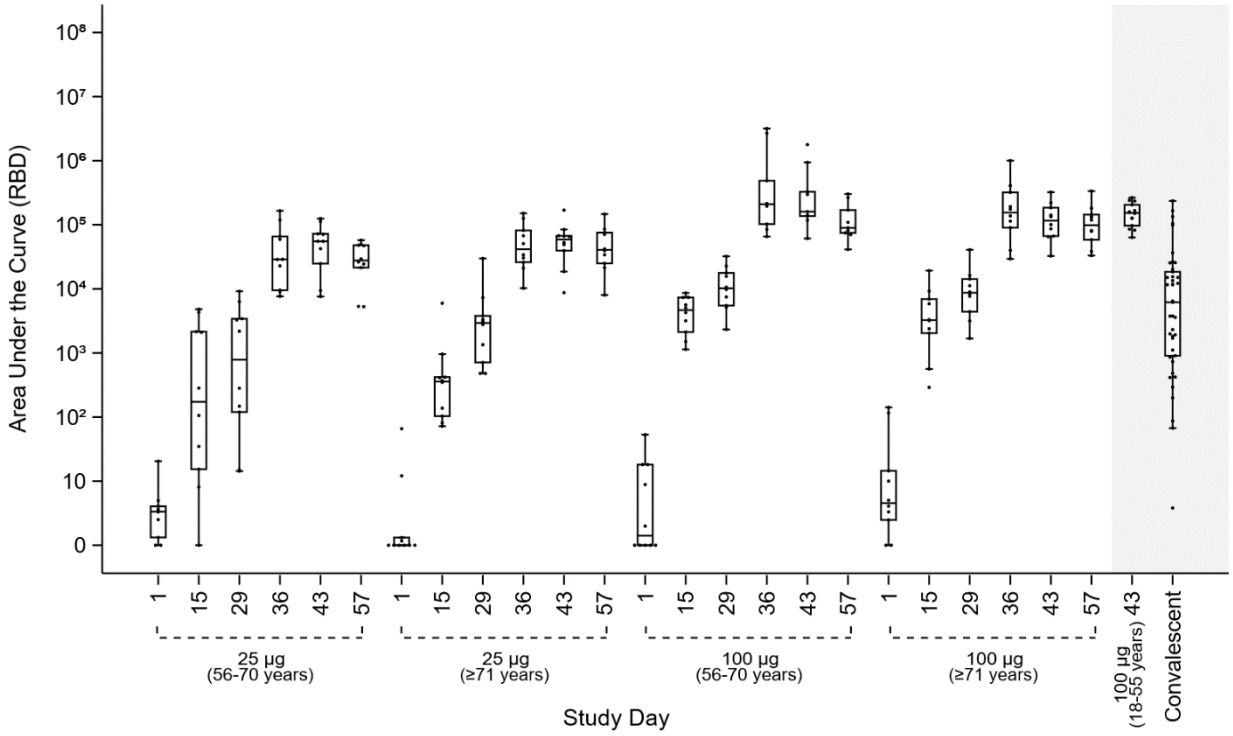


Figure S4. Pseudoneutralization (PsVNA) 614D responses by time point and vaccination group – ID_{80}.

Boxes and horizontal bars denote interquartile range (IQR) and median ID_{80}, respectively. Whisker endpoints are equal to the maximum and minimum values below or above the median +/- 1.5 x IQR. Data from 18-55 year-old subjects that received a 100 µg dose of mRNA-1273, and convalescent sera from 41 individuals are included for comparison (gray background).[3] Ten participants were tested at each time point in these older adults except for 9 participants in the 25 µg 56-70 year-old group beginning at Day 36.

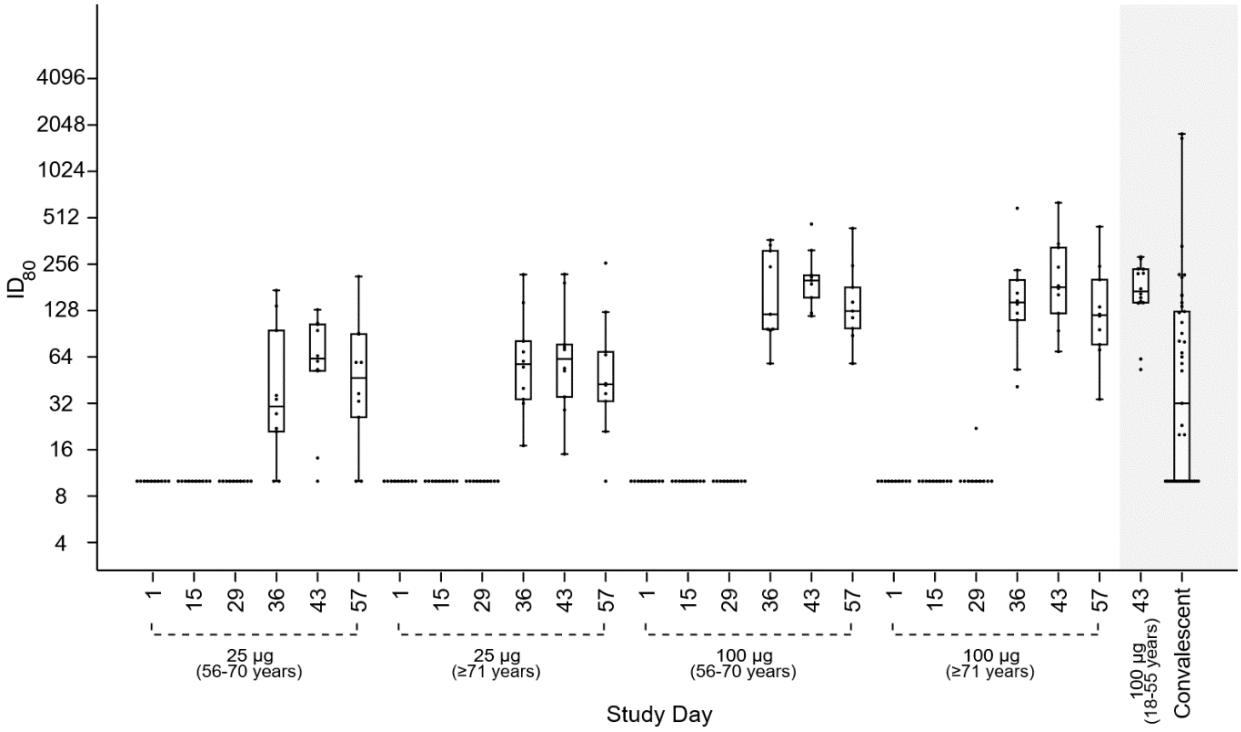
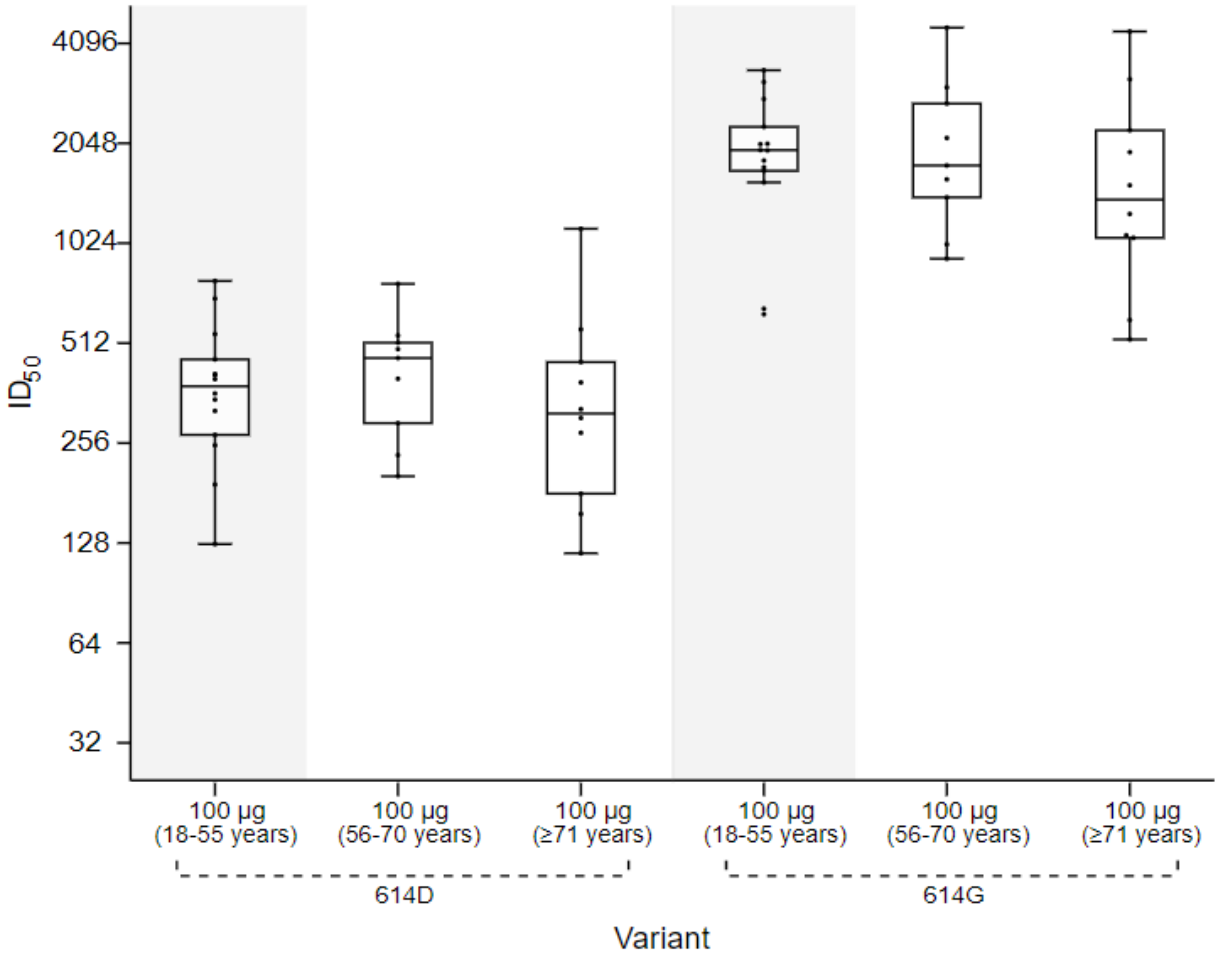


Figure S5. Pseudoneutralization (PsVNA) Comparison of 614D and 614G at Day 43.

Boxes and horizontal bars denote interquartile range (IQR) and median ID_{80} at Day 43, respectively. Whisker endpoints are equal to the maximum and minimum values below or above the median +/- 1.5 x IQR. Results from 18-55 year old subjects that received a 100 µg dose of mRNA-1273 are included for comparison (gray background).[3] Panel **A** represents the PsVNA ID_{50}, Panel **B** represents the PsVNA ID_{80}. Ten participants were tested at each time point in these older adults.

A.



B.

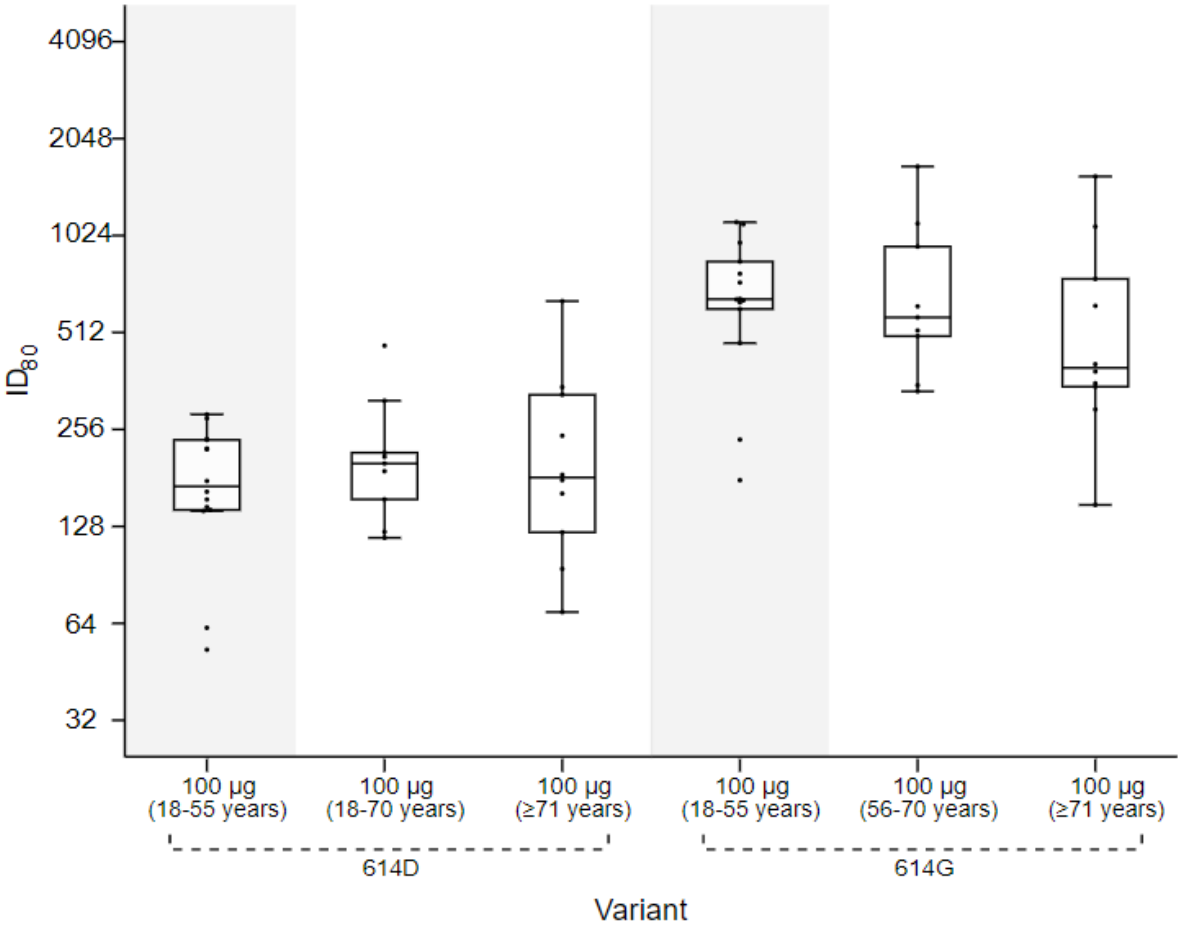
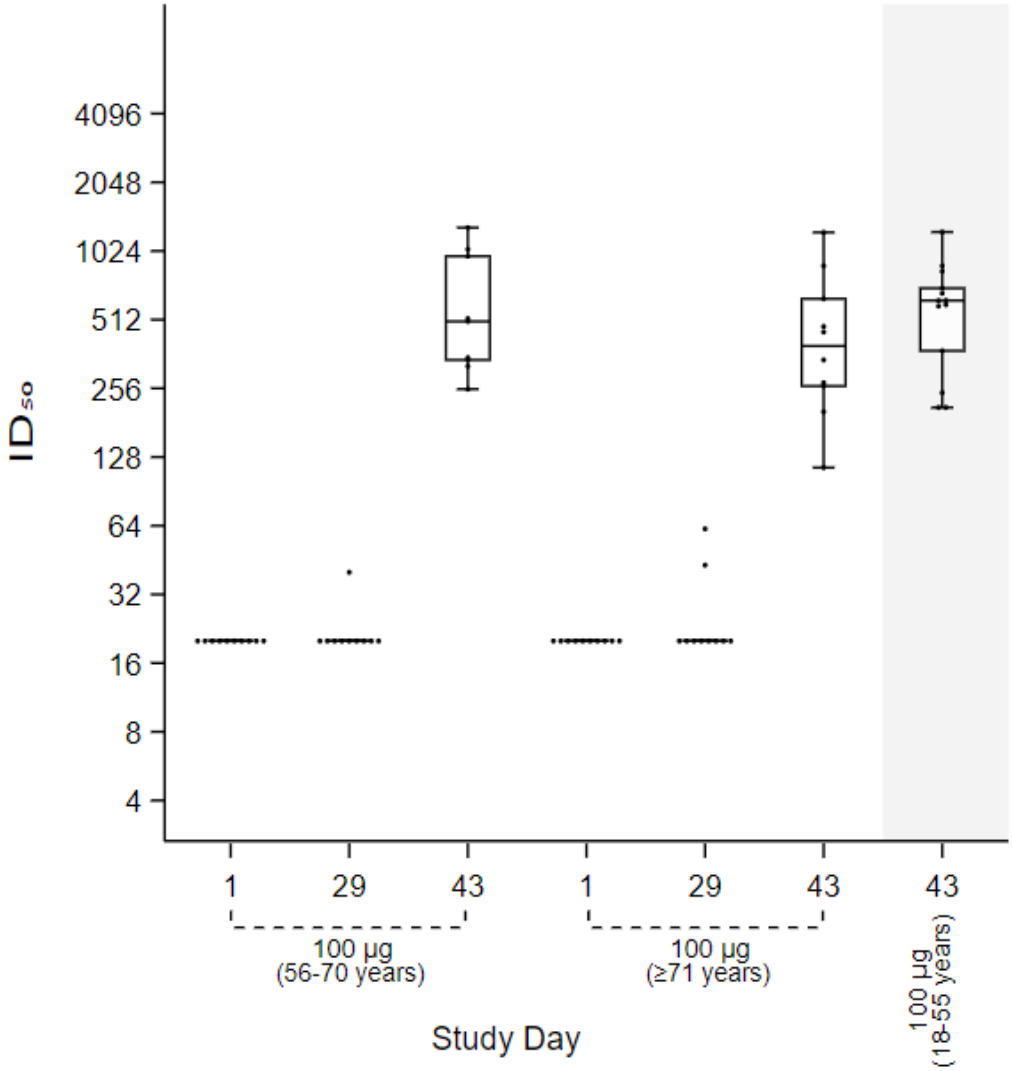

4096
2048
1024
512
256
128
64
32
ID80
100 µg (18-55 years)
100 µg (18-70 years)
100 µg (≥71 years)
100 µg (18-55 years)
100 µg (56-70 years)
100 µg (≥71 years)
614D
614G
Variant

Figure S6. Nanoluciferase high throughput neutralization assay (nLuc HTNA)

Boxes and horizontal bars denote interquartile range (IQR) and median ID_{80} at Day 43, respectively. Whisker endpoints are equal to the maximum and minimum values below or above the median +/- 1.5 x IQR. Results from 18-55 year-old subjects that received a 100 µg dose of mRNA-1273 are included for comparison (gray background).[3] Panel **A** represents the nLuc HTNA ID_{50}. Panel **B** represents the nLUC HTNA ID_{80}. Ten participants were tested at each time point in these older adults.

A.



B.

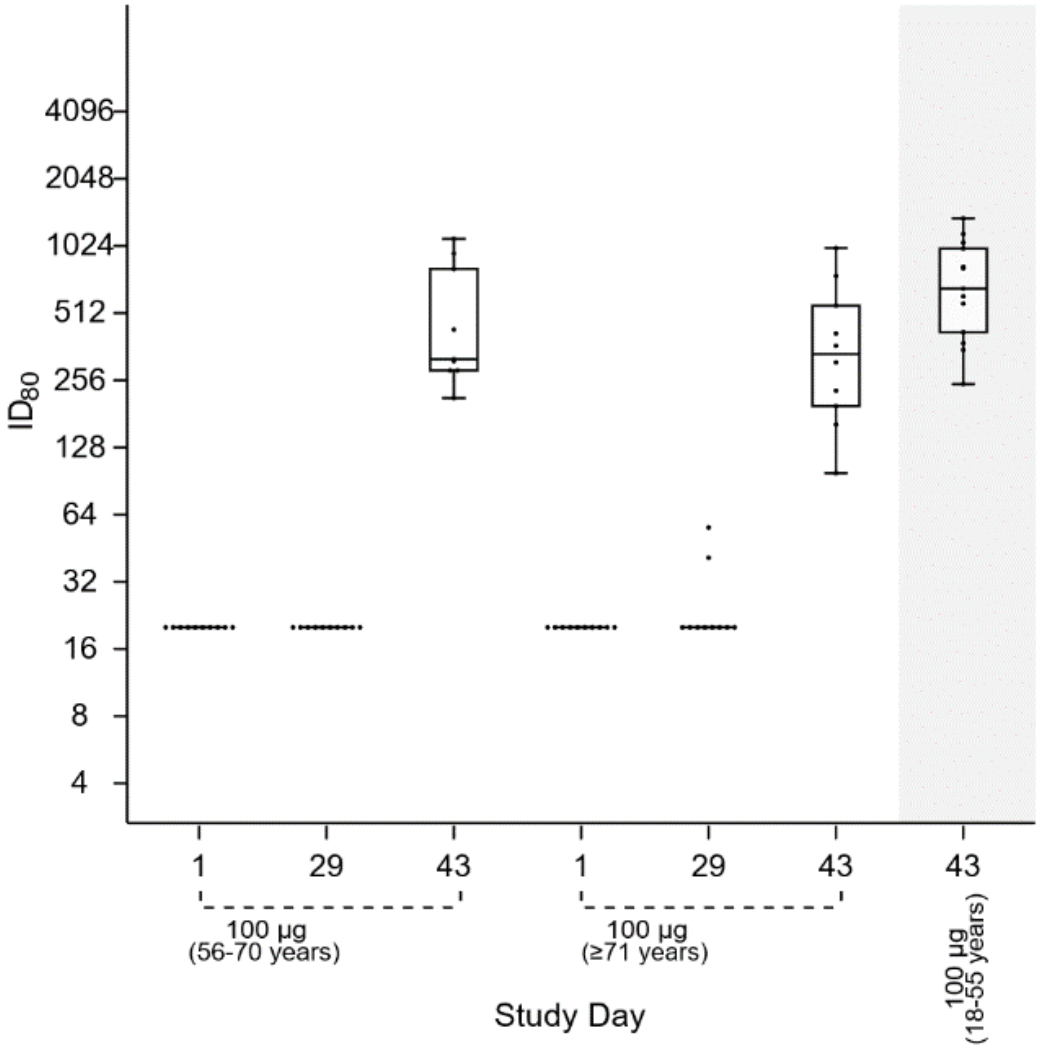

4096
2048
1024
512
256
128
64
32
16
8
4
ID80
1
29
43
1
29
43
43
100 µg
(56-70 years)
100 µg
(≥71 years)
100 µg
(18-55 years)
Study Day

Figure S7. FRNT-mNG ID_{80} responses

Boxes and horizontal bars denote interquartile range (IQR) and median ID_{80} at days 1, 29, and 43, respectively. Whisker endpoints are equal to the maximum and minimum values below or above the median +/- 1.5 x IQR. Results from 18-55 year old subjects that received a 100 µg dose of mRNA-1273 are included for comparison (gray background).[3] Ten participants were tested at each time point in these older adults except for 9 participants in the 25 µg 56-70 year-old group at Day 43.

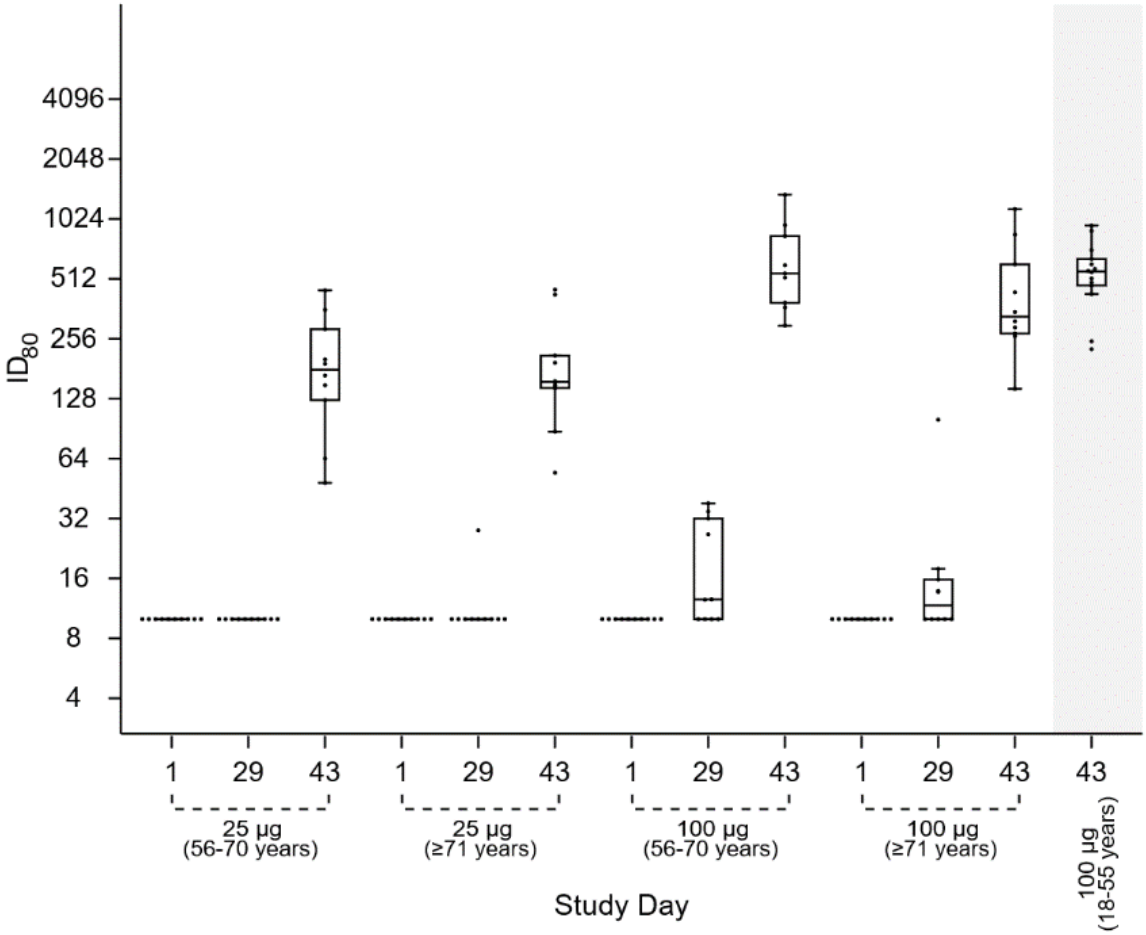
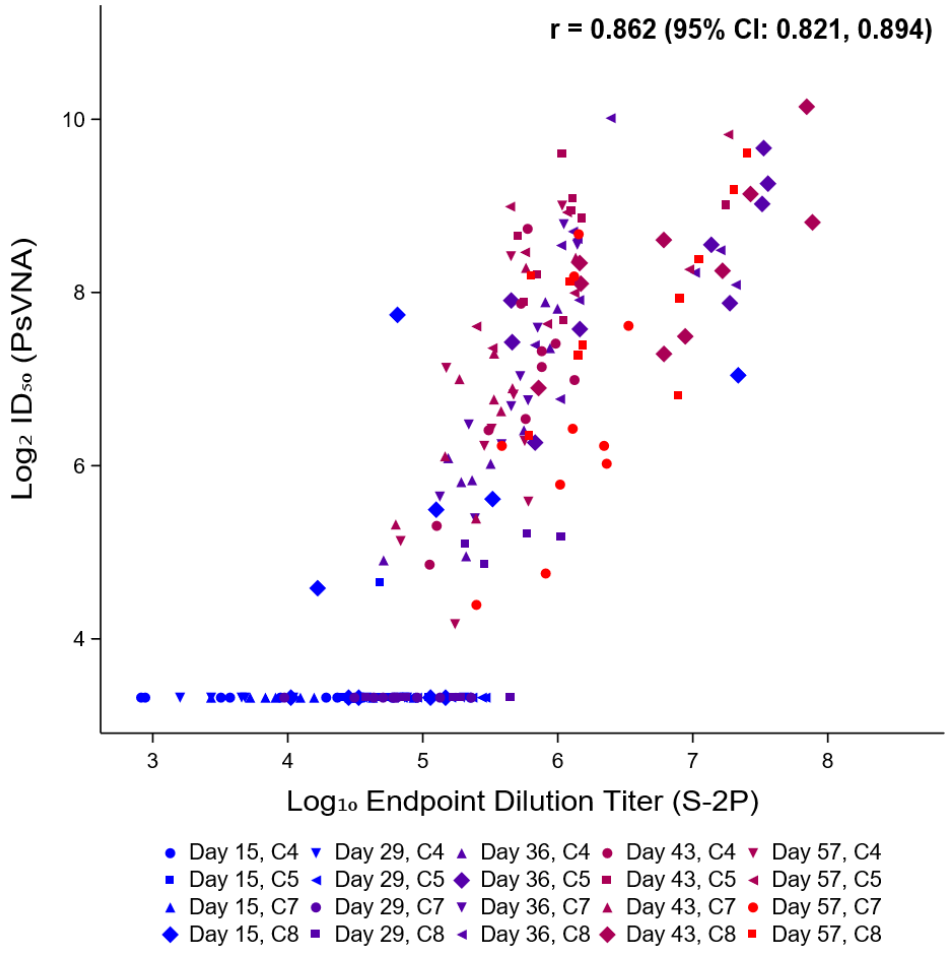


Figure S8. Correlation of SARS-CoV-2 spike ELISA endpoint dilution titers with neutralizing antibody titers

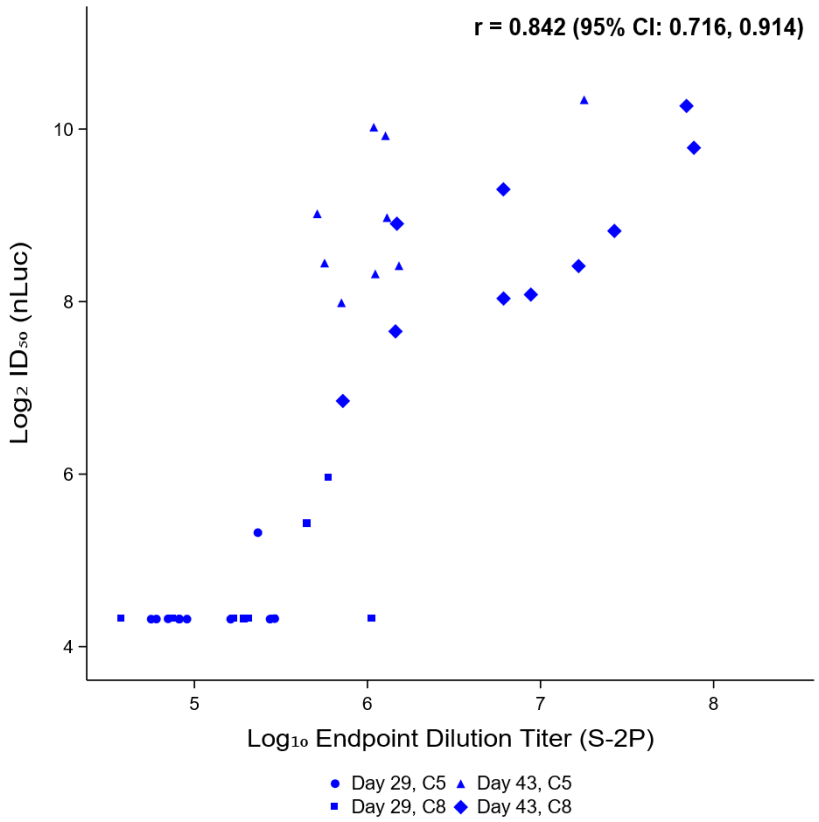
Panel **A**, vaccinee sera binding to S-2P expressed as endpoint dilution titer vs PseudoNeut ID_{50}. **B**, vaccinee sera binding to S-2P expressed as endpoint dilution titer vs nLUC HTNA ID_{50}. **C**, vaccinee sera binding to S-2P expressed as endpoint dilution titer vs FRNT-mNG ID_{50}. **D**, vaccinee sera binding to S-2P expressed as endpoint dilution titer vs $PRNT_{80}$. Spearman correlations were calculated for all post vaccination time points available. Confidence intervals were calculated using the z-transformation.

C4 is the 25 µg dose in 56-70 year-olds; C5 is the 100 µg dose in 56-70 year-olds; C7 is the 25 µg dose in ≥71 year-olds; and C8 is the 100 µg dose in ≥71 year-olds.

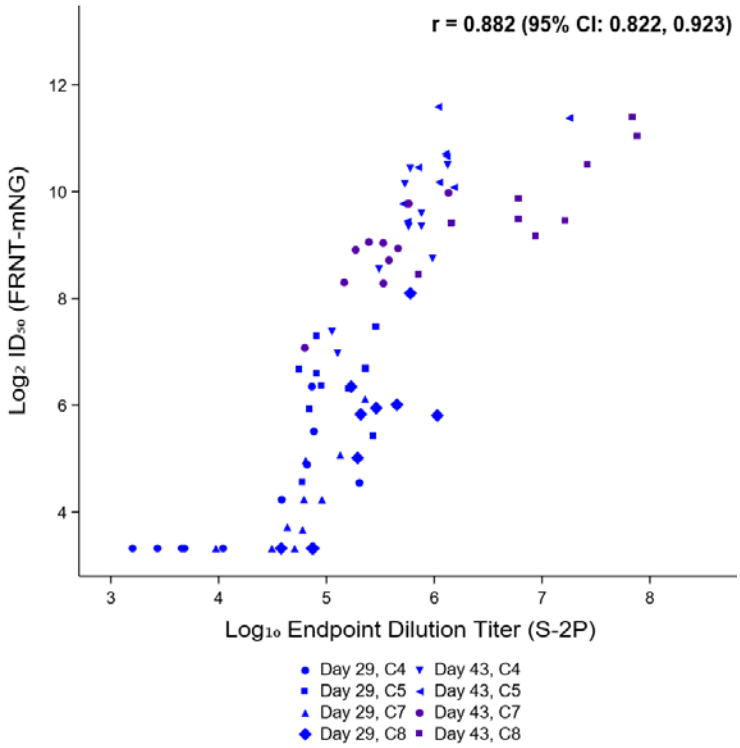
A.



B.


r = 0.842 (95% CI: 0.716, 0.914)
Log₂ ID₅₀ (nLuc)
10
8
6
4
5
6
7
8
Log₁₀ Endpoint Dilution Titer (S-2P)
Day 29, C5
Day 43, C5
Day 29, C8
Day 43, C8

C.


r = 0.882 (95% CI: 0.822, 0.923)
Log₂ ID₅₀ (FRNT-mNG)
12
10
8
6
4
3
4
5
6
7
8
Log₁₀ Endpoint Dilution Titer (S-2P)
Day 29, C4
Day 43, C4
Day 29, C5
Day 43, C5
Day 29, C7
Day 43, C7
Day 29, C8
Day 43, C8

D.

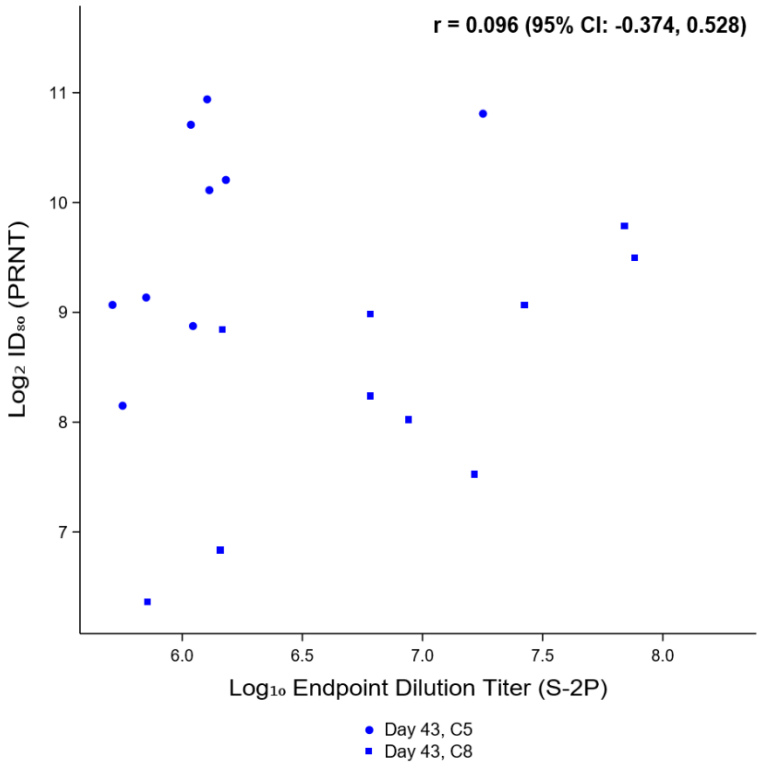
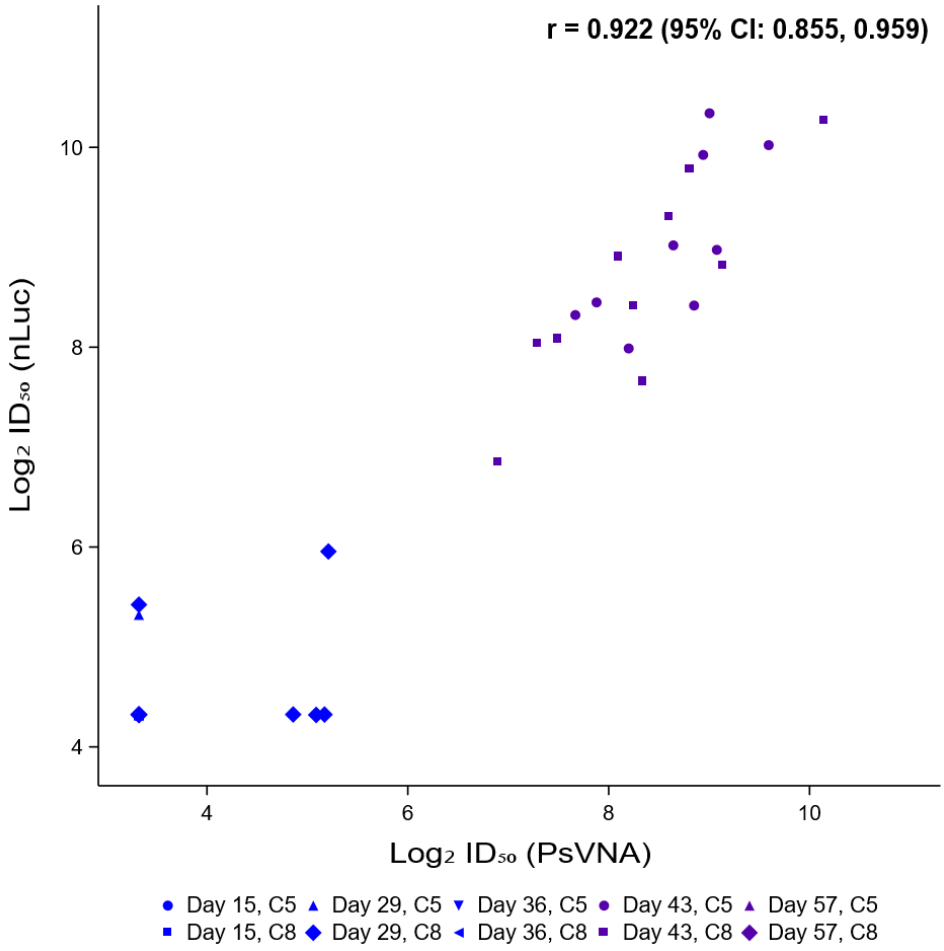

r = 0.096 (95% CI: -0.374, 0.528)
11
10
9
8
7
Log2 ID80 (PRNT)
6.0
6.5
7.0
7.5
8.0
Log10 Endpoint Dilution Titer (S-2P)
Day 43, C5
Day 43, C8

Figure S9. PsVNA correlation with other live-virus neutralization assays.

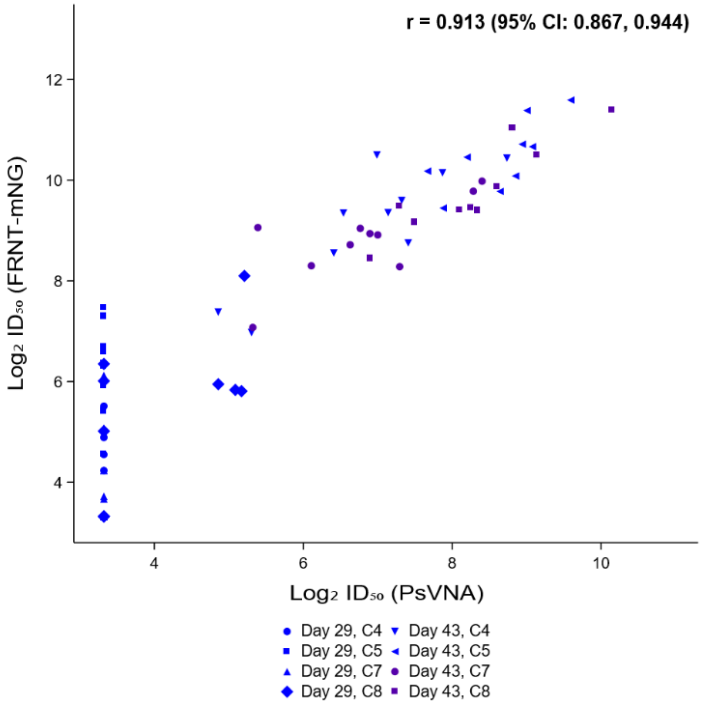
Panel **A**, vaccinee sera PsVNA (ID_{50}) vs NanoLuc ID_{50}. **B**, vaccinee sera PsVNA (ID_{50}) vs FRNT ID_{50}. **C**, PsVNA ID_{50} versus PRNT ID_{80}. Spearman correlations were calculated for all post vaccination time points available. Confidence intervals were calculated using the z-transformation.

C4 is the 25 µg dose in 56-70 year-olds; C5 is the 100 µg dose in 56-70 year-olds; C7 is the 25 µg dose in ≥71 year-olds; and C8 is the 100 µg dose in ≥71 year-olds.

A.



B.


r = 0.913 (95% CI: 0.867, 0.944)
Log2 ID50 (FRNT-mNG)
Log2 ID50 (PsVNA)
Day 29, C4
Day 43, C4
Day 29, C5
Day 43, C5
Day 29, C7
Day 43, C7
Day 29, C8
Day 43, C8

C.

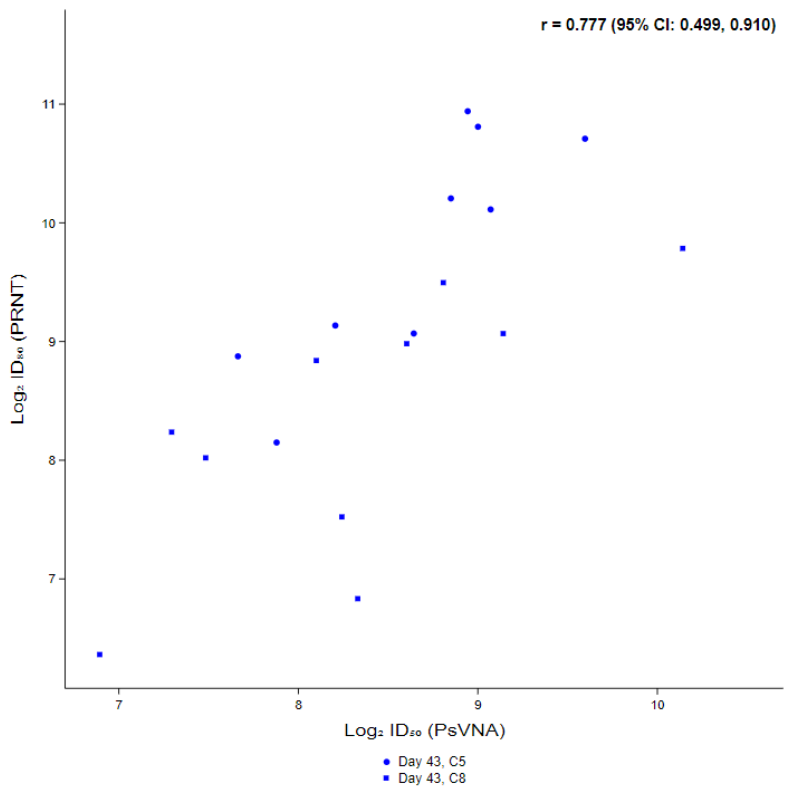
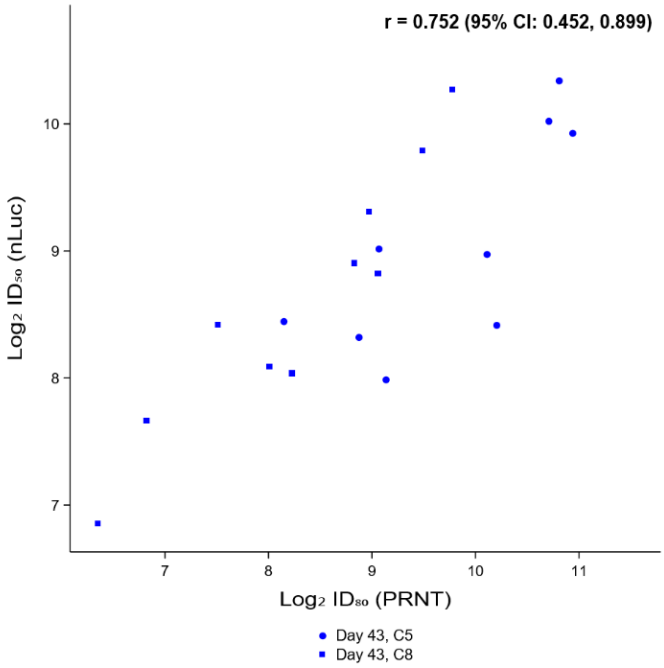

r = 0.777 (95% CI: 0.499, 0.910)
Log2 ID90 (PRNT)
Log2 ID50 (PsVNA)
Day 43, C5
Day 43, C8

Figure S10. $PRNT_{80}$ correlation with other live-virus neutralization assays.

Panel A, vaccinee sera $PRNT_{80}$ vs nLuc ID_{50} at Day 43. Panel B. vaccinee sera $PRNT_{80}$ vs FRNT-mNG ID_{50} at Day 43. Spearman correlations were calculated for all post vaccination time points available. Confidence intervals were calculated using the z-transformation.

C5 is the 100 µg dose in 56-70 year-olds; and C8 is the 100 µg dose in ≥71 year-olds.

A.



B.

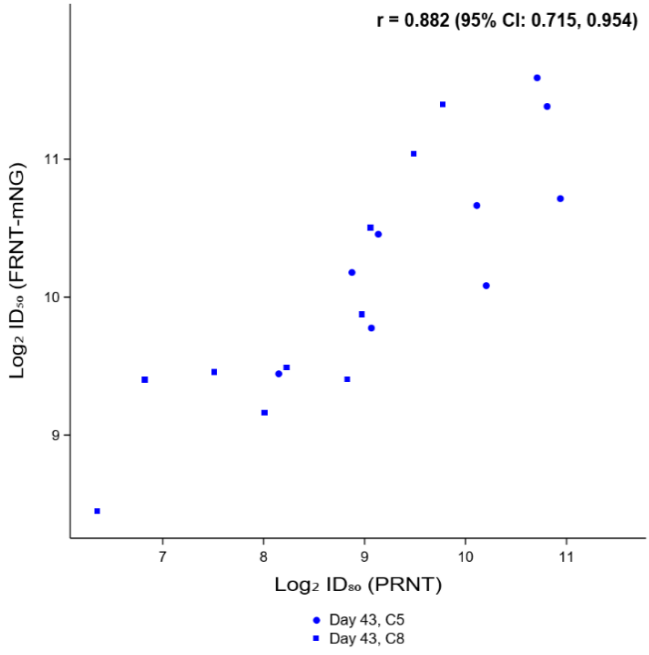


Figure S11. Live-virus neutralization nLuc ID_{50} correlation with FRNT-mNG ID_{50}.

Values shown are for days 29 and 43 specimens after receiving 100 µg mRNA-1273. nLuc ID_{50} versus FRNT-mNG ID_{50}. Spearman correlations were calculated for all post vaccination time points available. Confidence intervals were calculated using the z-transformation.

C5 is the 100 µg dose in 56-70 year-olds; and C8 is the 100 µg dose in ≥71 year-olds.

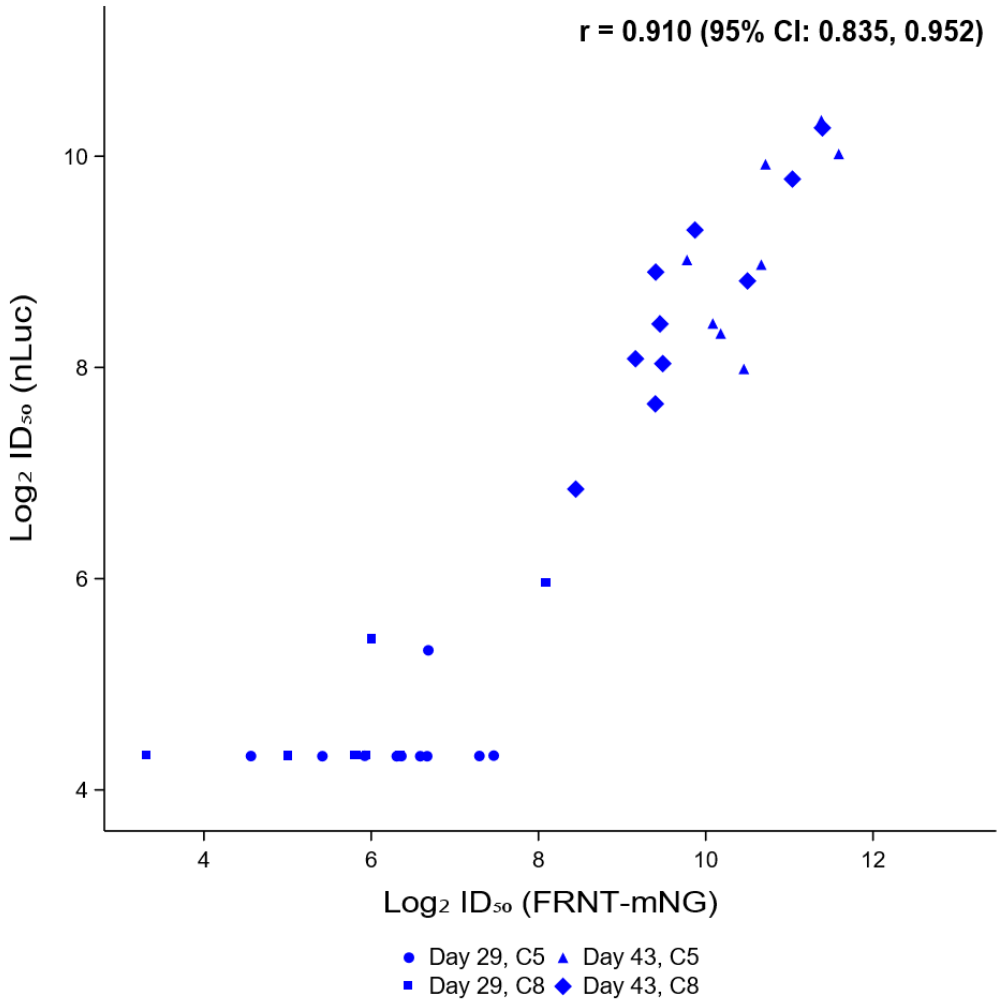


Figure S12. Heatmap Correlation between assays

Heatmap of Spearman correlations and 95% confidence intervals between the assays. Confidence intervals were calculated using the z-transformation.

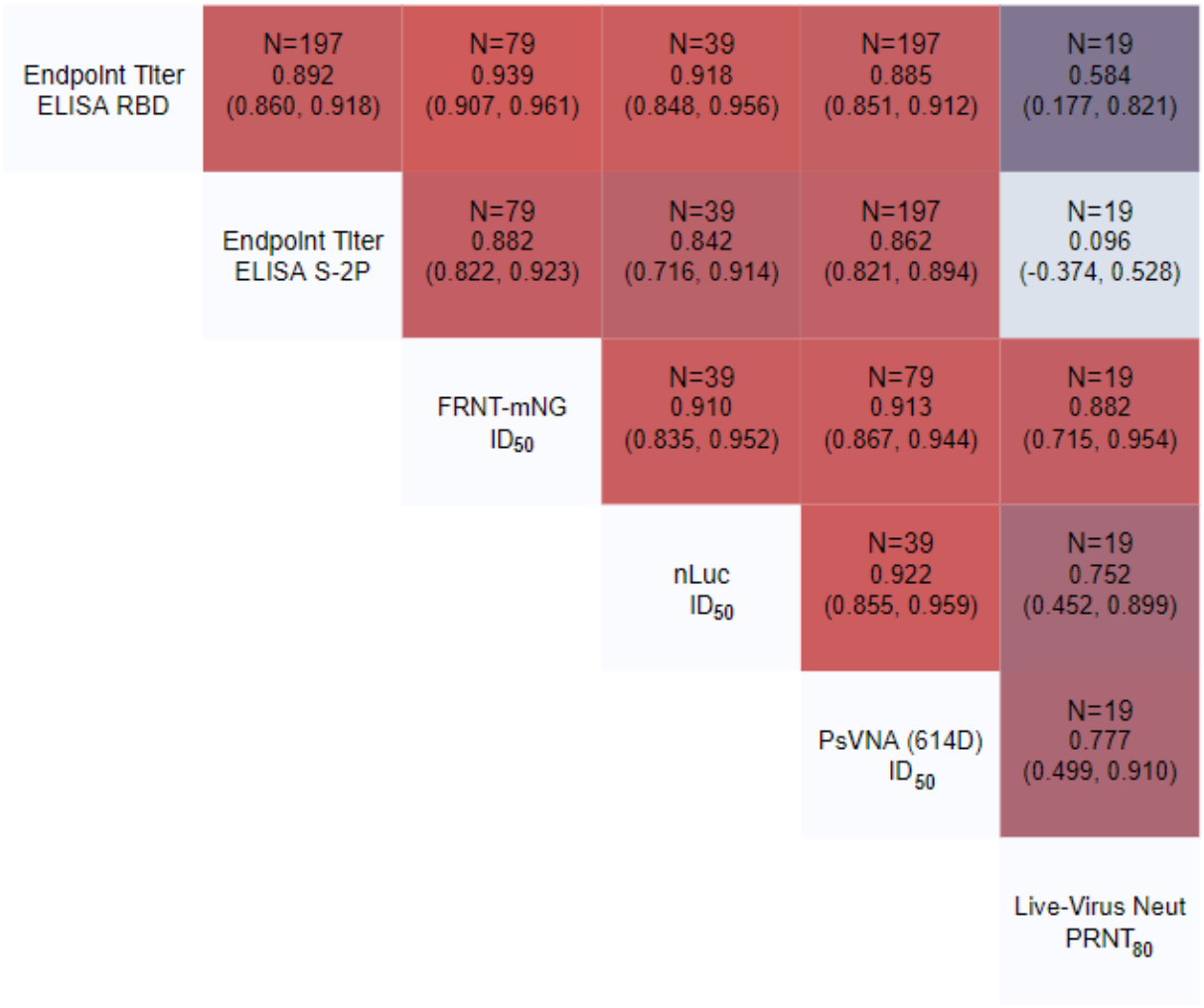


Fig S13. mRNA-1273-specific CD4 T cell responses (S2 peptide pool).

Frequencies of CD4 T cells producing the indicated cytokines from 25 µg 56-70 year-old or ≥71 year-old dose groups and from the 100 µg 56-70 year-old or ≥71 year-old dose groups following stimulation with SARS-CoV-2 S2 peptide pool. For Th1 responses (**A**) red circles indicate any combination of IFN-γ, IL-2 and TNF, blue squares indicate IFN-γ, green triangles indicate IL-2, and orange diamonds indicate TNF. For Th2 cytokine responses (**B**), red circles indicate any combination of IL-4 and IL-13, blue squares indicate IL-4, and green triangles indicate IL-13. Ten participants were tested at each time point in these older adults except for 9 participants in the 25 µg 56-70 year-old group at Day 43. The boxes indicate interquartile ranges (see Additional Statistical Methods section within the Supplement).

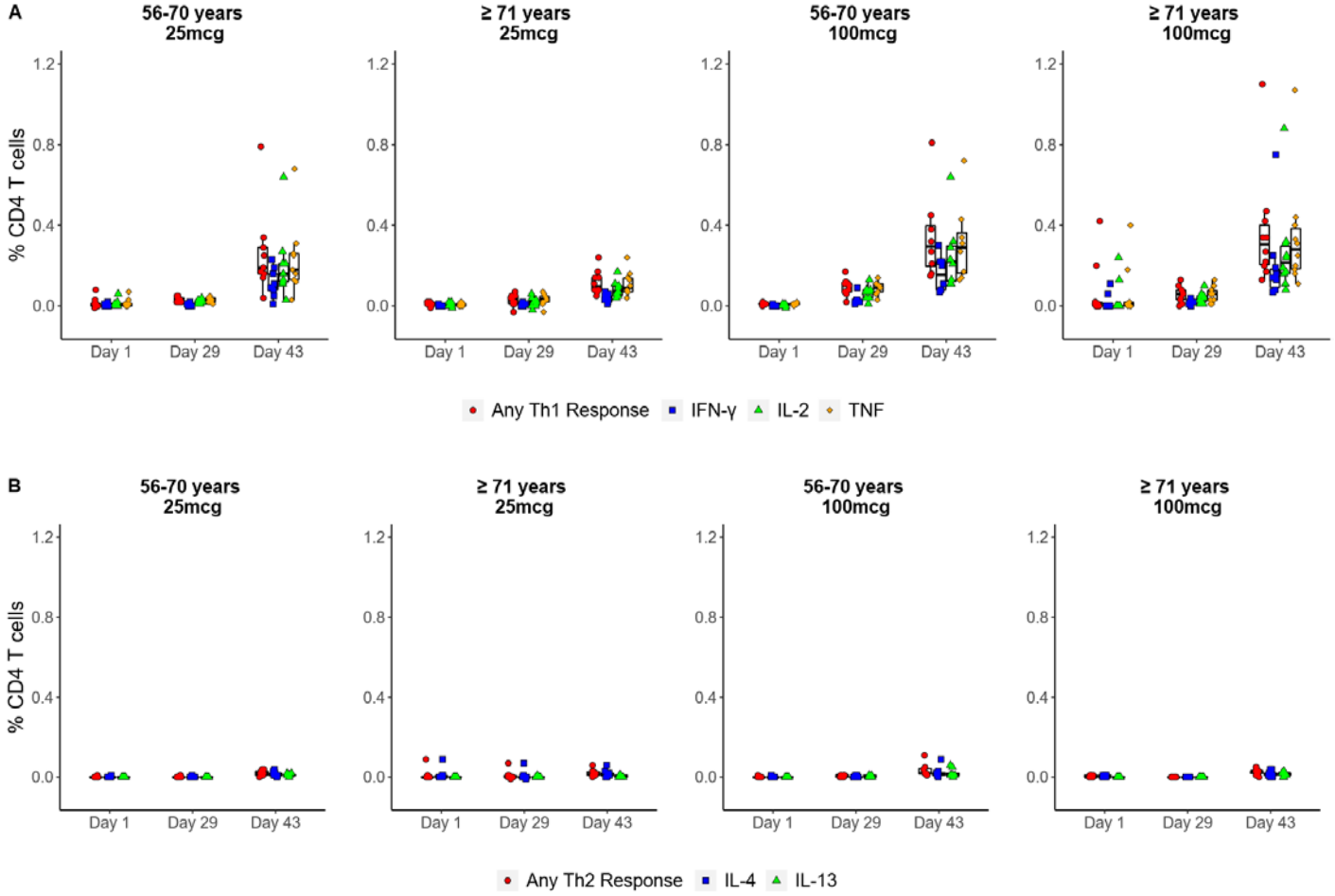


Fig S14. mRNA-1273-specific CD8 T cell responses.

Frequencies of CD8 T cells producing the indicated cytokines from 25µg 56-70 year-old or ≥71 year-old dose groups and the 100 µg 56-70 year-old or ≥71 year-old dose groups following stimulation with SARS-CoV-2 S1 peptide pool (**A**) or SARS-CoV-2 S2 peptide pool (**B**). Red circles indicate any combination of IFN-γ, IL-2 and TNF, blue squares indicate IFN-γ, green triangles indicate IL-2, and orange diamonds indicate TNF. Ten participants were tested at each time point in these older adults except for 9 participants in the 25 µg 56-70 year-old group at Day 43. The boxes indicate interquartile ranges (see Additional Statistical Methods section within the Supplement).

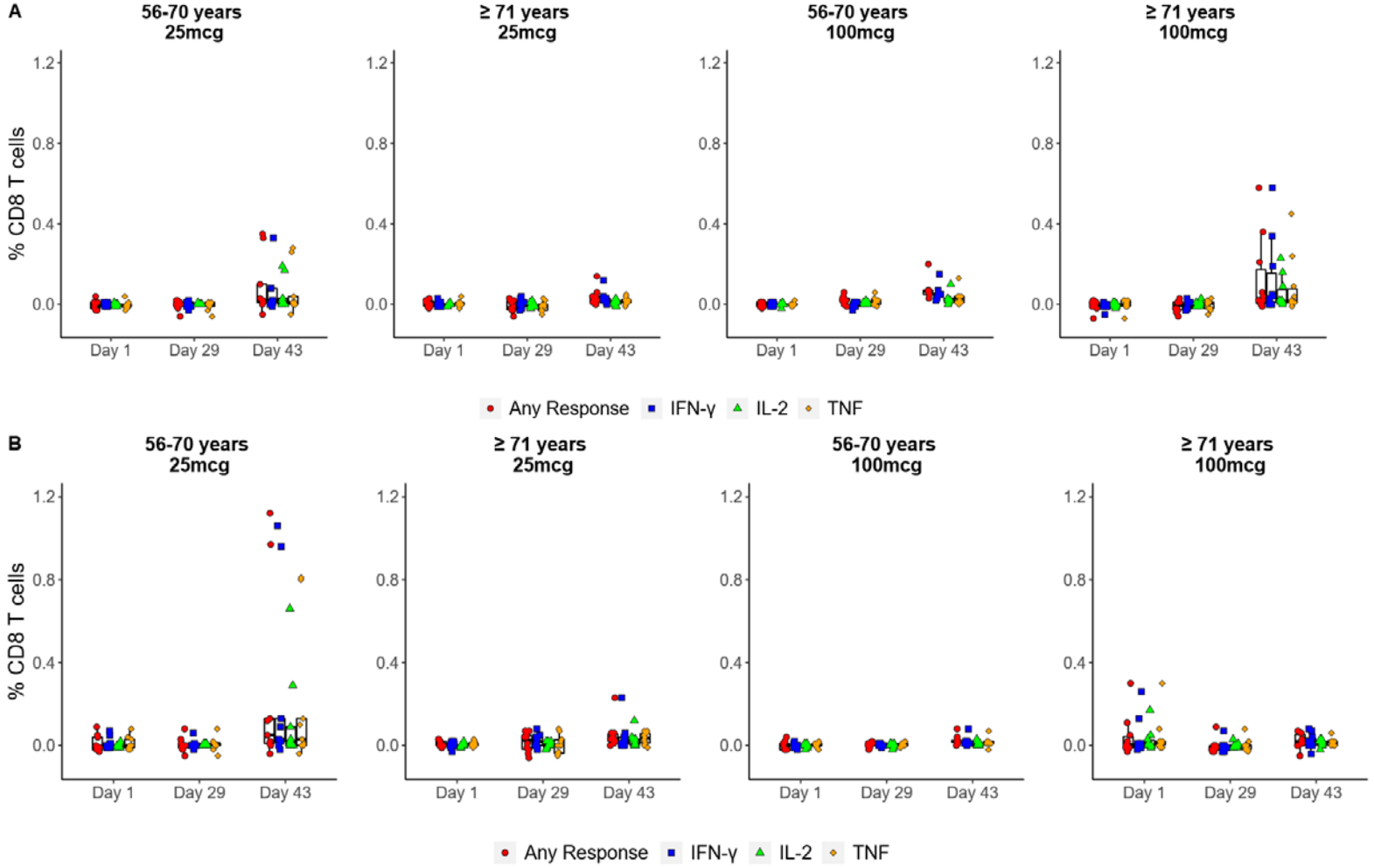


Table S1. Toxicity grading scales for solicited systemic and local adverse events*.

	Mild	Moderate	Severe
Arthralgia	No interference with activity	Some interference with activity	Significant; prevents daily activity
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity
Fever	38.0°C – 38.4°C	38.5°C – 38.9°C	39.0°C - 40°C
Chills	No interference with activity	Some interference with activity	Significant; prevents daily activity
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity
Nausea	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration
Size (diameter) of erythema/redness	2.5 – 5 cm	5.1 – 10 cm	> 10 cm
Size (diameter) of induration/swelling	2.5 – 5 cm	5.1 – 10 cm	> 10 cm
Pain (at injection site)	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity

*Obtained from a standard toxicity grading scale.[10]

Table S2. Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Vaccination Group

			None			Mild			Moderate			Severe		
Symptom	**Dose**	**Vaccination Group**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Any Systemic Symptom	**Dose 1**	**25 µg (18-55 years)**	10	66.7	38.4, 88.2	3	20.0	4.3, 48.1	2	13.3	1.7, 40.5	-	-	
		25 µg (56-70 years)	5	50.0	18.7, 81.3	3	30.0	6.7, 65.2	2	20.0	2.5, 55.6	-	-	
		25 µg (≥71 years)	5	50.0	18.7, 81.3	5	50.0	18.7, 81.3	-	-		-	-	
		100 µg (18-55 years)	5	33.3	11.8, 61.6	8	53.3	26.6, 78.7	2	13.3	1.7, 40.5	-	-	
		100 µg (56-70 years)	7	70.0	34.8, 93.3	3	30.0	6.7, 65.2	-	-		-	-	
		100 µg (≥71 years)	7	70.0	34.8, 93.3	3	30.0	6.7, 65.2	-	-		-	-	
	Dose 2	**25 µg (18-55 years)**	6	46.2	19.2, 74.9	4	30.8	9.1, 61.4	3	23.1	5, 53.8	-	-	
		25 µg (56-70 years)	3	30.0	6.7, 65.2	5	50.0	18.7, 81.3	1	10.0	0.3, 44.5	1	10.0	0.3, 44.5
		25 µg (≥71 years)	7	70.0	34.8, 93.3	3	30.0	6.7, 65.2	-	-		-	-	
		100 µg (18-55 years)	-	-		3	20.0	4.3, 48.1	12	80.0	51.9, 95.7	-	-	
		100 µg (56-70 years)	1	11.1	0.3, 48.2	3	33.3	7.5, 70.1	5	55.6	21.2, 86.3	-	-	
		100 µg (≥71 years)	3	30.0	6.7, 65.2	3	30.0	6.7, 65.2	3	30.0	6.7, 65.2	1	10.0	0.3, 44.5
Any Local Symptom	**Dose 1**	**25 µg (18-55 years)**	5	33.3	11.8, 61.6	10	66.7	38.4, 88.2	-	-		-	-	
		25 µg (56-70 years)	5	50.0	18.7, 81.3	5	50.0	18.7, 81.3	-	-		-	-	
		25 µg (≥71 years)	4	40.0	12.2, 73.8	6	60.0	26.2, 87.8	-	-		-	-	
		100 µg (18-55 years)	1	6.7	0.2, 31.9	11	73.3	44.9, 92.2	2	13.3	1.7, 40.5	1	6.7	0.2, 31.9
		100 µg (56-70 years)	2	20.0	2.5, 55.6	8	80.0	44.4, 97.5	-	-		-	-	
		100 µg (≥71 years)	2	20.0	2.5, 55.6	8	80.0	44.4, 97.5	-	-		-	-	
	Dose 2	**25 µg (18-55 years)**	3	23.1	5, 53.8	9	69.2	38.6, 90.9	1	7.7	0.2, 36	-	-	
		25 µg (56-70 years)	4	40.0	12.2, 73.8	4	40.0	12.2, 73.8	2	20.0	2.5, 55.6	-	-	
		25 µg (≥71 years)	3	30.0	6.7, 65.2	5	50.0	18.7, 81.3	2	20.0	2.5, 55.6	-	-	
		100 µg (18-55 years)	-	-		10	66.7	38.4, 88.2	4	26.7	7.8, 55.1	1	6.7	0.2, 31.9

			None			Mild			Moderate			Severe		
Symptom	**Dose**	**Vaccination Group**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
		100 µg (56-70 years)	1	11.1	0.3, 48.2	6	66.7	29.9, 92.5	2	22.2	2.8, 60	-	-	
		100 µg (≥71 years)	-	-		6	60.0	26.2, 87.8	4	40.0	12.2, 73.8	-	-	

Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.
N=All subjects receiving Dose 1 with any solicited event data recorded in the database.
Data for the 18 – 55 year old group are provided for reference.[3]

Table S3. Number of unsolicited, non-serious, adverse events classified by MedDRA® System Organ Class, severity, and investigator-assigned relationship to study vaccination.

		Subjects 56 – 70 Years (n = 20)		Subjects ≥71 years (n = 20)	
MedDRA System Organ Class	**Severity**	**Not Related (n)**	**Related (n)**	**Not Related (n)**	**Related (n)**
Any SOC	**Mild**	11	2	34	14
	Moderate	6	1	2	-
	Severe	1	-	-	-
Cardiac Disorders	**Mild**	-	-	2	-
	Moderate	-	-	-	-
	Severe	-	-	-	-
Ear And Labyrinth Disorders	**Mild**	-	1	-	-
	Moderate	-	-	-	-
	Severe	-	-	-	-
Gastrointestinal Disorders	**Mild**	1	-	-	-
	Moderate	-	-	-	-
	Severe	-	-	-	-
General Disorders And Administration Site Conditions	**Mild**	2	-	6	5
	Moderate	-	-	-	-
	Severe	-	-	-	-
Infections And Infestations	**Mild**	-	-	1	-
	Moderate	2	-	-	-
	Severe	-	-	-	-
Injury, Poisoning And Procedural Complications	**Mild**	1	-	15	-
	Moderate	2	-	-	-
	Severe	-	-	-	-
Metabolism And Nutrition Disorders	**Mild**	-	-	-	-
	Moderate	-	1	-	-
	Severe	1	-	-	-
Musculoskeletal And Connective Tissue Disorders	**Mild**	1	-	3	-
	Moderate	-	-	2	-
	Severe	-	-	-	-
Nervous System Disorders	**Mild**	3	-	1	3
	Moderate	-	-	-	-
	Severe	-	-	-	-
Psychiatric Disorders	**Mild**	-	1	-	3
	Moderate	-	-	-	-
	Severe	-	-	-	-

		Subjects 56 – 70 Years (n = 20)		Subjects ≥71 years (n = 20)	
MedDRA System Organ Class	**Severity**	**Not Related (n)**	**Related (n)**	**Not Related (n)**	**Related (n)**
Respiratory, Thoracic And Mediastinal Disorders	**Mild**	2	-	-	-
	Moderate	1	-	-	-
	Severe	-	-	-	-
Skin And Subcutaneous Tissue Disorders	**Mild**	-	-	5	3
	Moderate	1	-	-	-
	Severe	-	-	-	-
Vascular Disorders	**Mild**	1	-	1	-
	Moderate	-	-	-	-
	Severe	-	-	-	-

Table S4. Geometric Mean Humoral Immunogenicity Assay Responses to mRNA-1273 in Study Participants and in Convalescent Serum Specimens

Time Point	25 µg 56-70 years		25 µg ≥71 years		100 µg 56-70 years		100 µg ≥71 years		100 µg 18–55 years^		Convalescent Sera^	
	No.	GM (95%CI)	No.	GM (95%CI)	No.	GM (95%CI)	No.	GM (95%CI)	No.	GM (95%CI)	No.	GMT (95%CI)
ELISA anti-S-2P Endpoint Titer											41	138,901 (82,876, 232,799
Day 1	10	189 (76, 466)	10	111 (55, 222)	10	655 (270, 1,591)	10	953 (493, 1,842)	15	131 (65, 266)		
Day 15	10	10,509 (2,841, 38,868)	10	14,837 (6,925, 31,787)	10	55,532 (40,611, 75,935)	10	84,383 (26,977, 263,943)	15	86,291 (56,403, 132,016)		
Day 29	10	17,684 (5,300, 59,001)	10	57,986 (31,452, 106,905)	10	115,831 (73,288, 183,069)	10	203,365 (97,384, 424,686)	15	109,209 (79,051, 150,874)		
Day 36	10	313,720 (160,451, 613,395)	10	460,094 (272,951, 775,548)	9	5,033,017 (1,113,760, 22,743,909)	10	2,636,979 (1,072,782, 6,481,893)	15	781,399 (606,247, 1,007,156)		
Day 43	10	476,136 (263,956, 858,874)	10	303,630 (167,743, 549,597)	9	1,305,996 (581,138, 2,934,971)	10	8,091,439 (2,546,249, 25,712,881)	14	811,119 (656,336, 1,002,404)		
Day 57	10	323,945 (182,202, 575,958)	10	1,128,391 (636,087, 2,001,717)	9	1,183,066 (379,698, 3,686,201)	10	3,638,522 (1,316,233, 10,058,130)	14	782,719 (619,310, 989,244)		
ELISA anti-RBD Endpoint Titer											41	37,244 (20,170, 68,771)
Day 1	10	204 (114, 365)	10	111 (46, 270)	10	223 (64, 775)	10	503 (174, 1,455)	15	166 (82, 337)		
Day 15	10	2,924 (576, 14,833)	10	4,676 (2,236, 9,777)	10	30,981 (15,901, 60,362)	10	25,670 (12,394, 53,168)	15	34,073 (21,688, 53,531)		
Day 29	10	4,841 (1,531, 15,304)	10	15,338 (7,085, 33,203)	10	45,690 (26,314, 79,330)	10	56,343 (35,052, 90,567)	15	93,231 (59,895, 145,123)		

Day 36	10	198,643 (98,719, 399,707)	10	160,591 (82,611, 312,177)	9	1,471,882 (560,108, 3,867,893)	10	711,752 (368,657, 1,374,153)	15	499,539 (400,950, 622,370)		
Day 43	10	201,496 (115,918, 350,251)	10	295,194 (167,293, 520,878)	9	1,005,639 (445,521, 2,269,948)	10	694,471 (465,032, 1,037,111)	14	558,905 (462,908, 674,810)		
Day 57	10	78,045 (42,847, 142,159)	10	218,268 (106,743, 446,314)	9	506,364 (235,654, 1,088,051)	10	453,506 (255,624, 804,573)	14	371,271 (266,721, 516,804)		
PsVNA 614D ID50											41	106 (60, 189)
Day 1	10	10 (NE)	10	10 (NE)	10	10 (NE)	10	10 (NE)	15	10 (NE)		
Day 15	10	10 (NE)	10	10 (NE)	10	11 (9, 13)	10	26 (11, 60)	15	24 (13, 42)		
Day 29	10	10 (NE)	10	10 (NE)	10	10 (NE)	10	16 (10, 26)	15	18 (12, 27)		
Day 36	10	79 (47, 135)	10	121 (69, 211)	9	289 (164, 507)	10	310 (202, 475)	15	263 (188, 368)		
Day 43	10	116 (66, 205)	10	112 (67, 188)	9	402 (289, 560)	10	317 (198, 508)	14	360 (273, 476)		
Day 57	10	92 (45, 188)	10	86 (44, 171)	9	324 (212, 496)	10	242 (147, 399)	14	267 (186, 385)		
PsVNA 614G ID50												
Day 43	-	-	-	-	9	1,878 (1,259, 2,801)	10	1,456 (895, 2,368)	14	1,796 (1,350, 2,391)		
Nanoluciferase Neutralization Assay – ID50												
Day 1		-	-	-	10	20 (NE)	10	20 (NE)	15	10 (NE)		
Day 29		-	-	-	10	21 (18, 25)	10	24 (18, 32)	15	29 (19, 44)		
Day 43		-	-	-	9	530 (337, 835)	10	391 (235, 649)	13	526 (374, 739)		
FRNT-mNG ID50												
Day 1	10	10 (NE)	10	10 (NE)	10	10 (NE)	10	10 (NE)	15	10 (NE)		
Day 29	10	19 (11, 32)	10	18 (12, 29)	10	80 (52, 123)	10	39 (18, 86)	15	69 (46, 102)		
Day 43	10	550 (302, 1,001)	10	448 (299, 672)	9	1,425 (980, 2,072)	10	900 (575, 1,409)	14	1,388 (1,056, 1,825)		

PRNT-ID80											3	158 (15-1,663)
Day 1	-	-	-	-	10	4 (NE)	10	4 (NE)	15	4 (NE)		
Day 43	-	-	-	-	9	878 (516, 1,494)	10	317 (181, 557)	14	654 (460, 930)		

ELISA , enzyme-linked immunosorbent assay; GMT, geometric mean titer; RBD, receptor binding domain ID_{50}, 50% inhibitory dilution; ID_{80}, 80% inhibitory dilution; NE, not estimable; PsVNA, pseudotyped lentivirus reporter neutralization assay; FRNT-mNG, focus reduction neutralization test-mNeonGreen; PRNT, plaque reduction neutralization test.

^Data from 18-55 year-old subjects that received a 100 μg dose of mRNA-1273, and convalescent sera from 41 individuals are included for comparison.[3]

Table S5. Geometric Mean Humoral Immunogenicity Assay Responses to mRNA-1273 in Study Participants and in Convalescent Serum Specimens

Time Point	25 µg 56-70 years		25 µg ≥71 years		100 µg 56-70 years		100 µg ≥71 years		100 µg 18–55 years		Convalescent Sera^	
	No.	GM (95%CI)	No.	GM (95%CI)	No.	GM (95%CI)	No.	GM (95%CI)	No.	GM (95%CI)	No.	GMT (95%CI)
ELISA anti-S-2P AUC											41	14,157 (7,616, 26,312)
Day 1	10	2 (0, 5)	10	1 (0, 3)	10	9 (1, 37)	10	15 (6, 39)	15	1 (0, 4)		
Day 15	10	702 (103, 4,751)	10	1,664 (679, 4,076)	10	9,822 (6,539, 14,753)	10	12,040 (4,376, 33,122)	15	19,068 (12,424, 29,265)		
Day 29	10	2,037 (496, 8,355)	10	5,949 (2,934, 12,061)	10	20,493 (14,413, 29,137)	10	23,933 (10,375, 55,204)	15	20,525 (14,234, 29,595)		
Day 36	10	45,869 (23,165, 90,823)	10	95,566 (57,468, 158,922)	9	222,678 (143,857, 344,688)	10	243,246 (151,838, 389,681)	15	213,076 (165,185, 274,852)		
Day 43	10	64,533 (34,146, 121,959)	10	70,620 (41,797, 119,320)	9	205,650 (148,703, 284,406)	10	240,795 (151,610, 382,441)	14	221,956 (182,108, 270,524)		
Day 57	10	49,990 (27,060, 92,349)	10	92,536 (54,896, 155,984)	9	167,685 (105,544, 266,412)	10	183,823 (117,623, 287,282)	14	147,332 (113,898, 190,580)		
ELISA anti-RBD AUC											41	4,222 (2,021, 8,819)
Day 1	10	2 (1, 5)	10	1 (0, 5)	10	3 (0, 10)	10	6 (1, 24)	15	2 (0, 4)		
Day 15	10	161 (18, 1,341)	10	317 (122, 825)	10	3,817 (2,303, 6,327)	10	3,007 (1,219, 7,417)	15	5,642 (3,130, 10,170)		
Day 29	10	522 (91, 2,970)	10	2,354 (935, 5,927)	10	10,045 (5,718, 17,645)	10	8,229 (4,332, 15,630)	15	12,130 (8,447, 17,418)		

Day 36	10	31,501 (14,520, 68,343)	10	44,554 (24,426, 81,270)	9	172,194 (106,913, 277,336)	10	128,299 (70,950, 232,004)	15	126,250 (91,696, 173,824)		
Day 43	10	41,848 (21,034, 83,258)	10	48,343 (26,849, 87,043)	9	157,455 (105,180, 235,712)	10	111,806 (69,029, 181,092)	14	141,713 (110,096, 182,410)		
Day 57	10	24,347 (13,051, 45,416)	10	41,781 (23,064, 75,689)	9	109,975 (66,446, 182,018)	10	95,909 (57,611, 159,664)	14	106,248 (76,429, 147,701)		
PsVNA 614D ID_{80}											41	41 (26, 66)
Day 1	10	10 (NE)	10	10 (NE)	10	10 (NE)	10	10 (NE)	15	10 (NE)		
Day 15	10	10 (NE)	10	10 (NE)	10	10 (NE)	10	10 (NE)	15	13 (8, 19)		
Day 29	10	10 (NE)	10	10 (NE)	10	10 (NE)	10	11 (9, 13)	15	10 (10, 11)		
Day 36	10	36 (17, 74)	10	58 (34, 99)	9	158 (93, 267)	10	140 (82, 239)	15	134 (96, 188)		
Day 43	10	54 (29, 100)	10	61 (34, 110)	9	203 (145, 283)	10	194 (121, 311)	14	164 (122, 219)		
Day 57	10	43 (21, 85)	10	48 (25, 92)	9	140 (89, 222)	10	123 (73, 205)	14	141 (97, 204)		
PsVNA 614G ID_{80}												
Day 43	-	-	-	-	9	644 (427, 971)	10	482 (296, 787)	14	620 (457, 841)		
nLuciferase Neutralization Assay – ID_{80}												
Day 1			-	-	10	20 (NE)	10	20 (NE)	15	10 (NE)		
Day 29			-	-	10	20 (NE)	10	24 (18, 31)	15	32 (22, 46)		
Day 43			-	-	9	440 (276, 700)	10	327 (196, 546)	13	646 (472, 885)		
FRNT mNG ID_{80}												
Day 1	10	10 (NE)	10	10 (NE)	10	10 (NE)	10	10 (NE)	15	10 (NE)		
Day 29	10	10 (NE)	10	11 (9, 14)	10	17 (11, 25)	10	15 (9, 25)	15	25 (18, 33)		
Day 43	10	167 (101, 277)	10	169 (107, 268)	9	583 (400, 851)	10	392 (252, 609)	14	525 (416, 663)		

ELISA , enzyme-linked immunosorbent assay; GMT, geometric mean titer; RBD, receptor binding domain ID_{50}, 50% inhibitory dilution; ID_{80}, 80% inhibitory dilution; NE, not estimable; PsVNA, pseudotyped lentivirus reporter neutralization assay; FRNT-mNG, focus reduction neutralization test-mNeonGreen; PRNT, plaque reduction neutralization test.

^Data from 18-55 year-old subjects that received a 100 µg dose of mRNA-1273, and convalescent sera from 41 individuals are included for comparison.[3]

Table S6. Mean Percentages of CD4 T cells expressing cytokines with 95% CI with 95% Confidence Intervals by Time Point and Vaccination Group - Th1 Response

S6a. Day 1 (Pre-Vaccination 1)

Simulation	Cell Type	Statistic	25 mcg mRNA-1273 56-70 years (N=10)	25 mcg mRNA-1273 ≥71 years (N=10)	100 mcg mRNA-1273 56-70 years (N=10)	100 mcg mRNA-1273 ≥71 years (N=10)
SARS-CoV-2 S1	**Any Th1**	n	9	10	9	10
		Mean	-0.001	0.004	0.008	0.004
		95% CI	-0.012, 0.010	-0.004, 0.012	-0.002, 0.018	-0.002, 0.010
	IFNγ	n	9	10	9	10
		Mean	-0.001	-0.001	0.001	0.001
		95% CI	-0.004, 0.001	-0.005, 0.003	-0.001, 0.004	-0.001, 0.003
	IL-2	n	9	10	9	10
		Mean	0.000	0.005	-0.001	0.000
		95% CI	-0.007, 0.007	0.000, 0.010	-0.004, 0.001	-0.003, 0.003
	TNF	n	9	10	9	10
		Mean	-0.001	0.004	0.008	0.004
		95% CI	-0.011, 0.009	0.000, 0.008	0.000, 0.015	-0.001, 0.009
SARS-CoV-2 S2	**Any Th1**	n	9	10	9	10
		Mean	0.014	0.010	0.010	0.066
		95% CI	-0.006, 0.035	0.003, 0.017	0.006, 0.014	-0.033, 0.165
	IFNγ	n	9	10	9	10
		Mean	0.003	0.001	0.001	0.017
		95% CI	-0.002, 0.009	-0.001, 0.003	-0.001, 0.004	-0.010, 0.044
	IL-2	n	9	10	9	10
		Mean	0.012	0.004	0.002	0.037
		95% CI	-0.003, 0.027	-0.003, 0.011	-0.003, 0.007	-0.022, 0.096

Simulation	Cell Type	Statistic	25 mcg mRNA-1273 56-70 years (N=10)	25 mcg mRNA-1273 ≥71 years (N=10)	100 mcg mRNA-1273 56-70 years (N=10)	100 mcg mRNA-1273 ≥71 years (N=10)
	TNF	n	9	10	9	10
		Mean	0.014	0.007	0.010	0.063
		95% CI	-0.003, 0.032	0.001, 0.013	0.006, 0.014	-0.030, 0.156

Note: N=Number of Subjects.
n=Number of subjects with results available at time point.
NE=Not Estimable

S6b. Day 29 (Pre-Vaccination 2)

Simulation	Cell Type	Statistic	25 mcg mRNA-1273 56-70 years (N=10)	25 mcg mRNA-1273 ≥71 years (N=10)	100 mcg mRNA-1273 56-70 years (N=10)	100 mcg mRNA-1273 ≥71 years (N=10)
SARS-CoV-2 S1	**Any Th1**	n	9	10	9	10
		Mean	0.037	0.023	0.102	0.069
		95% CI	0.020, 0.053	0.003, 0.043	0.078, 0.126	0.022, 0.116
	IFNγ	n	9	10	9	10
		Mean	0.007	0.001	0.022	0.016
		95% CI	0.001, 0.012	-0.003, 0.005	0.012, 0.033	0.003, 0.029
	IL-2	n	9	10	9	10
		Mean	0.026	0.014	0.072	0.046
		95% CI	0.013, 0.038	0.000, 0.028	0.052, 0.092	0.012, 0.080
	TNF	n	9	10	9	10
		Mean	0.033	0.023	0.096	0.066
		95% CI	0.017, 0.050	0.003, 0.043	0.076, 0.115	0.021, 0.111
SARS-CoV-2 S2	**Any Th1**	n	9	10	9	10
		Mean	0.031	0.028	0.093	0.058
		95% CI	0.021, 0.041	0.008, 0.048	0.061, 0.126	0.029, 0.087
	IFNγ	n	9	10	9	10
		Mean	0.008	0.005	0.029	0.014
		95% CI	0.003, 0.013	0.000, 0.010	0.011, 0.047	0.006, 0.022
	IL-2	n	9	10	9	10
		Mean	0.023	0.018	0.067	0.040
		95% CI	0.016, 0.031	0.002, 0.034	0.041, 0.093	0.021, 0.059
	TNF	n	9	10	9	10
		Mean	0.030	0.031	0.089	0.057
		95% CI	0.020, 0.040	0.011, 0.051	0.064, 0.114	0.029, 0.085

Simulation	Cell Type	Statistic	25 mcg mRNA-1273 56-70 years (N=10)	25 mcg mRNA-1273 ≥71 years (N=10)	100 mcg mRNA-1273 56-70 years (N=10)	100 mcg mRNA-1273 ≥71 years (N=10)
Note: N=Number of Subjects. n=Number of subjects with results available at time point. NE=Not Estimable						

S6c. Day 43 Post Vaccination 1 (14 Days Post Vaccination 2)

Simulation	Cell Type	Statistic	25 mcg mRNA-1273 56-70 years (N=10)	25 mcg mRNA-1273 ≥71 years (N=10)	100 mcg mRNA-1273 56-70 years (N=10)	100 mcg mRNA-1273 ≥71 years (N=10)
SARS-CoV-2 S1	**Any Th1**	n	9	10	8	10
		Mean	0.264	0.095	0.336	0.317
		95% CI	0.096, 0.433	0.061, 0.129	0.196, 0.476	0.162, 0.472
	IFNγ	n	9	10	8	10
		Mean	0.108	0.031	0.148	0.164
		95% CI	0.062, 0.153	0.016, 0.046	0.101, 0.194	0.077, 0.251
	IL-2	n	9	10	8	10
		Mean	0.204	0.065	0.224	0.214
		95% CI	0.074, 0.335	0.042, 0.088	0.122, 0.325	0.110, 0.318
	TNF	n	9	10	8	10
		Mean	0.224	0.085	0.296	0.295
		95% CI	0.085, 0.364	0.050, 0.120	0.176, 0.416	0.145, 0.445
SARS-CoV-2 S2	**Any Th1**	n	9	10	8	10
		Mean	0.263	0.116	0.344	0.366
		95% CI	0.097, 0.430	0.075, 0.157	0.164, 0.524	0.166, 0.566
	IFNγ	n	9	10	8	10
		Mean	0.112	0.039	0.160	0.198
		95% CI	0.059, 0.166	0.025, 0.053	0.088, 0.232	0.054, 0.342
	IL-2	n	9	10	8	10
		Mean	0.209	0.081	0.255	0.271
		95% CI	0.074, 0.344	0.053, 0.109	0.109, 0.401	0.108, 0.434
	TNF	n	9	10	8	10
		Mean	0.236	0.110	0.314	0.345
		95% CI	0.092, 0.379	0.068, 0.152	0.151, 0.477	0.148, 0.542

Simulation	Cell Type	Statistic	25 mcg mRNA-1273 56-70 years (N=10)	25 mcg mRNA-1273 ≥71 years (N=10)	100 mcg mRNA-1273 56-70 years (N=10)	100 mcg mRNA-1273 ≥71 years (N=10)
Note: N=Number of Subjects. n=Number of subjects with results available at time point. NE=Not Estimable						

Table S7. Mean Percentages of CD4 T cells expressing cytokines with 95% CI with 95% Confidence Intervals by Time Point and Vaccination Group - Th2 Response

S7a. Day 1 (Pre-Vaccination 1)

Simulation	Cell Type	Statistic	25 mcg mRNA-1273 56-70 years (N=10)	25 mcg mRNA-1273 ≥71 years (N=10)	100 mcg mRNA-1273 56-70 years (N=10)	100 mcg mRNA-1273 ≥71 years (N=10)
SARS-CoV-2 S1	**Any Th2**	n	9	10	9	10
		Mean	0.001	0.009	0.000	0.002
		95% CI	-0.001, 0.004	-0.007, 0.025	NE	-0.001, 0.005
	IL-13	n	9	10	9	10
		Mean	0.001	0.009	0.001	0.002
		95% CI	-0.001, 0.004	-0.007, 0.025	-0.001, 0.004	-0.001, 0.005
	IL-4	n	9	10	9	10
		Mean	0.000	0.000	0.000	0.000
		95% CI	NE	NE	NE	NE
SARS-CoV-2 S2	**Any Th2**	n	9	10	9	10
		Mean	0.001	0.010	0.001	0.004
		95% CI	-0.001, 0.004	-0.010, 0.030	-0.001, 0.004	0.000, 0.008
	IL-13	n	9	10	9	10
		Mean	0.001	0.011	0.001	0.004
		95% CI	-0.001, 0.004	-0.009, 0.031	-0.001, 0.004	0.000, 0.008
	IL-4	n	9	10	9	10
		Mean	0.000	0.000	0.000	0.000
		95% CI	NE	NE	NE	NE

Note: N=Number of Subjects.
n=Number of subjects with results available at time point.
NE=Not Estimable

S7b. Day 29 (Pre-Vaccination 2)

Simulation	Cell Type	Statistic	25 mcg mRNA-1273 56-70 years (N=10)	25 mcg mRNA-1273 ≥71 years (N=10)	100 mcg mRNA-1273 56-70 years (N=10)	100 mcg mRNA-1273 ≥71 years (N=10)
SARS-CoV-2 S1	**Any Th2**	n	9	10	9	10
		Mean	0.000	0.012	0.002	0.002
		95% CI	NE	-0.008, 0.032	-0.001, 0.006	-0.001, 0.005
	IL-13	n	9	10	9	10
		Mean	0.000	0.011	0.000	0.002
		95% CI	NE	-0.009, 0.031	NE	-0.001, 0.005
	IL-4	n	9	10	9	10
		Mean	0.000	0.000	0.000	0.000
		95% CI	NE	NE	NE	NE
SARS-CoV-2 S2	**Any Th2**	n	9	10	9	10
		Mean	0.002	0.008	0.006	0.000
		95% CI	-0.001, 0.006	-0.008, 0.024	0.002, 0.010	NE
	IL-13	n	9	10	9	10
		Mean	0.001	0.007	0.002	0.000
		95% CI	-0.001, 0.004	-0.009, 0.023	-0.001, 0.006	NE
	IL-4	n	9	10	9	10
		Mean	0.000	0.001	0.003	0.000
		95% CI	NE	-0.001, 0.003	-0.001, 0.007	NE

Note: N=Number of Subjects.
n=Number of subjects with results available at time point.
NE=Not Estimable

S7c. Day 43 Post Vaccination 1 (14 Days Post Vaccination 2)

Simulation	Cell Type	Statistic	25 mcg mRNA-1273 56-70 years (N=10)	25 mcg mRNA-1273 ≥71 years (N=10)	100 mcg mRNA-1273 56-70 years (N=10)	100 mcg mRNA-1273 ≥71 years (N=10)
SARS-CoV-2 S1	**Any Th2**	n	9	10	8	10
		Mean	0.022	0.015	0.029	0.023
		95% CI	0.012, 0.033	0.009, 0.021	0.010, 0.047	0.011, 0.035
	IL-13	n	9	10	8	10
		Mean	0.019	0.013	0.018	0.015
		95% CI	0.007, 0.031	0.007, 0.019	0.005, 0.030	0.008, 0.022
	IL-4	n	9	10	8	10
		Mean	0.010	0.005	0.021	0.015
		95% CI	0.006, 0.014	0.001, 0.009	0.008, 0.035	0.007, 0.023
SARS-CoV-2 S2	**Any Th2**	n	9	10	8	10
		Mean	0.021	0.020	0.035	0.027
		95% CI	0.011, 0.032	0.008, 0.032	0.007, 0.063	0.016, 0.038
	IL-13	n	9	10	8	10
		Mean	0.016	0.017	0.024	0.017
		95% CI	0.005, 0.026	0.004, 0.030	0.000, 0.047	0.007, 0.027
	IL-4	n	9	10	8	10
		Mean	0.011	0.005	0.020	0.016
		95% CI	0.006, 0.016	0.001, 0.009	0.002, 0.038	0.008, 0.024

Note: N=Number of Subjects.
n=Number of subjects with results available at time point.
NE=Not Estimable

Table S8. Mean Percentages of CD8 T cells expressing cytokines with 95% CI with 95% Confidence Intervals by Time Point and Vaccination Group

S8a. Day 1 (Pre-Vaccination 1)

Simulation	Cell Type	Statistic	25 mcg mRNA-1273 56-70 years (N=10)	25 mcg mRNA-1273 ≥71 years (N=10)	100 mcg mRNA-1273 56-70 years (N=10)	100 mcg mRNA-1273 ≥71 years (N=10)
SARS-CoV-2 S1	**Any CD8**	n	9	10	9	10
		Mean	-0.004	0.006	0.002	-0.005
		95% CI	-0.022, 0.013	-0.005, 0.017	-0.007, 0.011	-0.024, 0.014
	IFNγ	n	9	10	9	10
		Mean	-0.001	0.003	0.001	-0.008
		95% CI	-0.007, 0.005	-0.007, 0.013	-0.005, 0.007	-0.020, 0.004
	IL-2	n	9	10	9	10
		Mean	-0.001	-0.002	-0.001	-0.003
		95% CI	-0.006, 0.004	-0.007, 0.003	-0.007, 0.005	-0.010, 0.004
	TNF	n	9	10	9	10
		Mean	-0.003	0.004	0.000	-0.002
		95% CI	-0.019, 0.012	-0.007, 0.015	-0.007, 0.007	-0.021, 0.017
SARS-CoV-2 S2	**Any CD8**	n	9	10	9	10
		Mean	0.010	0.009	0.002	0.043
		95% CI	-0.021, 0.041	-0.002, 0.020	-0.014, 0.018	-0.028, 0.114
	IFNγ	n	9	10	9	10
		Mean	0.012	0.002	0.000	0.034
		95% CI	-0.010, 0.034	-0.009, 0.013	-0.009, 0.009	-0.031, 0.099
	IL-2	n	9	10	9	10
		Mean	0.000	0.001	-0.001	0.025
		95% CI	-0.008, 0.008	-0.005, 0.007	-0.008, 0.006	-0.014, 0.064
	TNF	n	9	10	9	10
		Mean	0.010	0.008	0.002	0.044

Simulation	Cell Type	Statistic	25 mcg mRNA-1273 56-70 years (N=10)	25 mcg mRNA-1273 ≥71 years (N=10)	100 mcg mRNA-1273 56-70 years (N=10)	100 mcg mRNA-1273 ≥71 years (N=10)
		95% CI	-0.016, 0.036	0.000, 0.016	-0.007, 0.011	-0.023, 0.111

Note: N=Number of Subjects.
n=Number of subjects with results available at time point.
NE=Not Estimable

S8b. Day 28 (Pre-Vaccination 2)

Simulation	Cell Type	Statistic	25 mcg mRNA-1273 56-70 years (N=10)	25 mcg mRNA-1273 ≥71 years (N=10)	100 mcg mRNA-1273 56-70 years (N=10)	100 mcg mRNA-1273 ≥71 years (N=10)
SARS-CoV-2 S1	**Any CD8**	n	9	10	9	10
		Mean	-0.004	-0.009	0.023	-0.010
		95% CI	-0.023, 0.014	-0.029, 0.011	0.007, 0.039	-0.030, 0.010
	IFNγ	n	9	10	9	10
		Mean	-0.002	0.002	0.000	-0.007
		95% CI	-0.014, 0.009	-0.013, 0.017	-0.011, 0.011	-0.021, 0.007
	IL-2	n	9	10	9	10
		Mean	0.001	-0.006	0.008	0.001
		95% CI	-0.001, 0.004	-0.015, 0.003	0.003, 0.013	-0.008, 0.010
	TNF	n	9	10	9	10
		Mean	-0.008	-0.011	0.017	-0.004
		95% CI	-0.026, 0.010	-0.029, 0.007	0.001, 0.033	-0.022, 0.014
SARS-CoV-2 S2	**Any CD8**	n	9	10	9	10
		Mean	0.003	0.015	0.003	-0.005
		95% CI	-0.024, 0.031	-0.018, 0.048	-0.006, 0.013	-0.030, 0.020
	IFNγ	n	9	10	9	10
		Mean	0.004	0.022	0.002	-0.005
		95% CI	-0.013, 0.022	0.000, 0.044	-0.003, 0.007	-0.025, 0.015
	IL-2	n	9	10	9	10
		Mean	0.003	0.002	0.000	0.001
		95% CI	-0.001, 0.007	-0.009, 0.013	-0.008, 0.008	-0.008, 0.010
	TNF	n	9	10	9	10
		Mean	0.007	0.004	0.003	0.002
		95% CI	-0.020, 0.033	-0.029, 0.037	-0.004, 0.011	-0.020, 0.024

Simulation	Cell Type	Statistic	25 mcg mRNA-1273 56-70 years (N=10)	25 mcg mRNA-1273 ≥71 years (N=10)	100 mcg mRNA-1273 56-70 years (N=10)	100 mcg mRNA-1273 ≥71 years (N=10)
Note: N=Number of Subjects. n=Number of subjects with results available at time point. NE=Not Estimable						

S8c. Day 43 Post Vaccination 1 (14 Days Post Vaccination 2)

Simulation	Cell Type	Statistic	25 mcg mRNA-1273 56-70 years (N=10)	25 mcg mRNA-1273 ≥71 years (N=10)	100 mcg mRNA-1273 56-70 years (N=10)	100 mcg mRNA-1273 ≥71 years (N=10)
SARS-CoV-2 S1	**Any CD8**	n	9	10	8	10
		Mean	0.089	0.035	0.075	0.128
		95% CI	-0.025, 0.202	0.005, 0.065	0.031, 0.119	-0.014, 0.270
	IFNγ	n	9	10	8	10
		Mean	0.088	0.031	0.058	0.126
		95% CI	-0.020, 0.195	0.007, 0.055	0.024, 0.091	-0.012, 0.264
	IL-2	n	9	10	8	10
		Mean	0.047	0.008	0.029	0.056
		95% CI	-0.012, 0.105	-0.001, 0.017	0.003, 0.054	-0.001, 0.113
	TNF	n	9	10	8	10
		Mean	0.061	0.018	0.036	0.087
		95% CI	-0.032, 0.154	0.005, 0.031	0.002, 0.071	-0.018, 0.192
SARS-CoV-2 S2	**Any CD8**	n	9	10	8	10
		Mean	0.264	0.050	0.026	0.022
		95% CI	-0.080, 0.608	0.003, 0.097	0.006, 0.047	-0.004, 0.048
	IFNγ	n	9	10	8	10
		Mean	0.254	0.042	0.021	0.021
		95% CI	-0.077, 0.586	-0.007, 0.091	0.001, 0.042	-0.004, 0.046
	IL-2	n	9	10	8	10
		Mean	0.122	0.028	0.009	0.011
		95% CI	-0.049, 0.293	0.003, 0.053	-0.001, 0.018	0.000, 0.022
	TNF	n	9	10	8	10
		Mean	0.204	0.034	0.016	0.021
		95% CI	-0.060, 0.469	0.013, 0.055	-0.005, 0.037	0.005, 0.037

Simulation	Cell Type	Statistic	25 mcg mRNA-1273 56-70 years (N=10)	25 mcg mRNA-1273 ≥71 years (N=10)	100 mcg mRNA-1273 56-70 years (N=10)	100 mcg mRNA-1273 ≥71 years (N=10)
Note: N=Number of Subjects. n=Number of subjects with results available at time point. NE=Not Estimable						

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